

## CURRICULUM VITAE

### BIOGRAPHICAL

Name: Mark T. Gladwin, M.D., F.A.C.P. Birth Date: December 21, 1966  
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### EDUCATION and TRAINING

#### UNDERGRADUATE and GRADUATE:

1985-1991 University of Miami Honors Program B.S. and MD, 1991  
In Medical Education (6 year medical program)  
Miami, Florida

#### POSTGRADUATE:

1991-1994	Oregon Health Sciences University (OHSU) Department of Internal Medicine Portland, Oregon	Internship, Residency Program Director: Tom Cooney, MD
1994-1995	Oregon Health Sciences University (OHSU) Department of Internal Medicine Portland, Oregon	Chief Resident Program Director: Tom Cooney, MD
1995-1996	Warren G. Magnuson Clinical Center Critical Care Medicine Department National Institutes of Health Bethesda, MD	Critical Care Fellow
1995-2000	Commander US Public Health Service (0-5)	

1996-1998	University of Washington Pulmonary Division Seattle, Washington	Pulmonary-Critical Care Fellow
1998-2000	Warren G. Magnuson Clinical Center Critical Care Medicine Department Bethesda, MD	Senior Research Fellow
2001-2004	Critical Care Medicine Dept, Clinical Center Laboratory of Chemical Biology, NIDDK Cardiovascular Branch, NHLBI National Institutes of Health Bethesda, MD	Tenure Track Investigator Section Head, Sickle Cell/Nitric Oxide Therapeutic Section
2004 – 2005	Vascular Therapeutic Section Cardiovascular Branch, NHLBI Critical Care Medicine Department, Clinical Center Laboratory of Chemical Biology, NIDDK National Institutes of Health Bethesda, MD	Tenured Senior Investigator, Section Head
2005 – 2007	Vascular Medicine Branch, NHLBI  Critical Care Medicine Department, Clinical Center National Institutes of Health Bethesda, MD	Branch Chief  Senior Investigator
2006 – 2008	NHLBI Functional Genomics Core National Institutes of Health Bethesda, MD	Director
2007 – 2008	Pulmonary and Vascular Medicine Branch, NHLBI National Institutes of Health Bethesda, MD	Branch Chief Tenured Senior Investigator

2008-Present      Division Chief, Pulmonary, Allergy, and      Professor of Medicine  
Critical Care Medicine

Director, Vascular Medicine Institute (VMI)  
University of Pittsburgh

#### CERTIFICATION and LICENSURE

- American Board of Internal Medicine Certifying Examination, 1994
- Recertified Diplomat, American Board of Internal Medicine – valid through 2018
- Diplomat in Pulmonary Disease, American Board of Pulmonary Medicine 1998-2008
- Recertified in Pulmonary Disease, American Board of Pulmonary Medicine 2008-2018
- Diplomat in Critical Care Medicine, American Board of Critical Care Medicine 1999-2009
- Recertified in Critical Care Medicine, American Board of Pulmonary Medicine 2009-2019
- Medical Licenses:
  - Pennsylvania # MD434600 - active
  - Maryland #D0052428 - active
  - Oregon #MD17824 (expired in good standing 12/31/97)
  - Washington #ML20005389 (expired in good standing 7/31/97)
  - District of Columbia #MD30661 (expired in good standing 12/31/05)
- Advanced Trauma Life Support, 1997
- Advanced Cardiac Life Support, 1999 - Present

#### MEMBERSHIPS in PROFESSIONAL and SCIENTIFIC SOCIETIES

- Association of American Physicians (AAP) - 2009
- American Society of Clinical Investigations (ASCI)
  - Member 2006 - present
  - Elected to Council - 2010
- Alpha Omega Alpha-1995 - present
- American Thoracic Society - 1998-present
  - Scientific Advisory Committee - 2009-2010
- Association of American Physicians (AAP) - 2009
- Society of Critical Care Medicine - 1996-1999
- Nitric Oxide Society
- Oxygen Society
- American Society for Biochemistry and Molecular Biology - 2002-present
- American Society of Hematology - 2002-present
- Fellow, American College of Physicians - 2008-present - #0100415
- Society for Free Radical Biology and Medicine - 2002-present - #03431

- University of Pittsburgh Sleep Medicine Institute Internal Advisory Board
  - Fellow Pulmonary Vascular Research Institute-2010-present
  - Dickson Prize Committee - University of Pittsburgh School of Medicine - 2010
  - NIH Scientific Management Review Board (SMRB) - 2010
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## HONORS AND AWARDS

- Henry K. Stanford Merit Scholarship, Florida Honors Merit Scholarship, Florida Academic Merit Scholarship, University of Miami, 1985-1986.
  - Honors Program in Medical Education, University of Miami, Florida, 1991.
  - Alpha Omega Alpha, 1994.
  - American College of Physicians Winning and Finalist Abstract, Clinical Vignette Competition for Associates, 74th Annual Session, Washington, D.C., 1993.
  - First Place Clinical Vignette Presentation, Regional American College of Physicians Conference, Eugene, Oregon, 1993.
  - Oregon Health Sciences University House Staff Teaching Award (Awarded by House Staff), 1993, 1994, and 1995.
  - Achievement Medal, US Public Health Service, NIH, 1999.
  - NIH Fellows Award for Research Excellence (FARE 2000), 2000.
  - American Thoracic Society Travel Award; Awarded by the Respiratory Structure and Function Assembly; 96<sup>th</sup> International Conference, 2000.
  - American Heart Association Scientific Sessions Travel Award. Awarded by the Vascular Biology Assembly, 2000.
  - American Thoracic Society Travel Award; Awarded by the Respiratory Structure and Function Assembly; 97<sup>th</sup> International Conference, 2001.
  - Academic Medicine Mentor Award, Awarded by the Fellowship Program in Academic Medicine for Minority Students (sponsored by Bristol-Myers Squibb Co) for the mentorship of Karin R. Minter, 2001.
  - Distinguished Mentor Award, Awarded by the NIH Pre-IRTA committee for mentorship of Esther Vivas and Benjamin Yang, 2002.
  - Clinical Center Director's Award for 2002 (category of Science).
  - The NIH Director's Award for Mentoring in making contributions to understanding the role of nitric oxide in sickle cell anemia patients, 2006.
  - The NIH Merit Award in recognition for accomplishments in both basic and clinical sciences in the use of nitrite and NO in clinical applications, 2006.
  - Presented at the Nobel Forum, Karolinska Institutet as part of the series "Frontiers I Biomedical Research", Stockholm, Sweden, 2007.
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## PUBLICATIONS

### ABSTRACTS Available upon request

### REFERRED MANUSCRIPTS OF ORIGINAL RESEARCH (selected manuscripts annotated with significance of scientific contribution)

Citation Report: Over 1400 citations per year for 2008, 2009 and 2010; H index of 49; average citations per item: 23.74

1. **Gladwin MT**, Duell BP. Inappropriate thyroid gland ablation in patients with generalized resistance to thyroid hormone: a common sequella of a rare disorder. Archives of Internal Medicine 1996; 156: 106-109.
2. Yao XL, Cowan MJ, **Gladwin MT**, Lawrence MM, Angus CW, Shelhamer JH. Dexamethasone alters arachidonate release from human epithelial cells by induction of p11 protein synthesis and inhibition of phospholipase A2 activity. Journal of Biological Chemistry 1999;274:17202-8.
3. **Gladwin MT**, Slonim A, Landucci DL, Gutierrez DC, Cunnion RE. Cannulation of the internal jugular vein: Is post-procedural chest radiography always necessary? Critical Care Medicine 1999; 27:1819-23.
4. **Gladwin MT**, Schechter AN, Shelhamer JH, Pannell LK, Conway DA, Hrinczenko BW, Nichols JS, Pease-Fye ME, Noguchi CT, Rodgers GP, Ognibene FP. Inhaled nitric oxide augments nitric oxide transport on sickle cell hemoglobin without affecting oxygen affinity. Journal of Clinical Investigation 1999; 104:937-945.
5. **Gladwin MT**, Ognibene FP, Pannell LK, Nichols JS, Pease-Fye ME, Shelhamer JH, Schechter AN. Relative role of heme nitrosylation and  $\beta$ -cysteine 93 nitrosation in the transport and metabolism of nitric oxide by hemoglobin in the human circulation. Proceedings of the National Academy of Sciences 2000; 97: 9943-9948.
6. Hrinczenko BW, Alayash AI, Wink DA, **Gladwin MT**, Rodgers GP, Schechter AN. Effect of nitric oxide and nitric oxide donors on red blood cell oxygen transport. British Journal of Haematology 2000; 110:412-419.
7. **Gladwin MT**, Shelhamer JH, Schechter AN, Pease-Fye ME, Waclawiw MA, Panza JA, Ognibene FP, Cannon RO III . Role of circulating nitrite and S-nitrosohemoglobin in regulation

of regional blood flow in humans. Proceedings of the National Academy of Sciences 2000; 97:11482-11487.

**Reports the discovery that the nitrite anion is metabolized from artery to vein across the human forearm circulation and provides the first hypothesis that nitrite is a circulating storage pool for NO bioactivity, later confirmed to regulate blood flow and hypoxic vasodilation (Cosby Nature Medicine 2003) and the cellular resilience to low oxygen and ischemia (Duranski JCI 2005). Total times cited: 177**

8. Gladwin MT, Yao XL, Cowan M, Huang XL, Schneider R, Grant LR, Logun C, Shelhamer JH. Retinoic acid reduces p11 protein levels in a bronchial epithelial cells by a post-translational mechanism. American Journal of Physiology: Lung Cellular and Molecular Physiologoy 2000; 279: L1103-L1109.
9. Deem S, Gladwin MT, Berg JT, Kerr ME, Swenson ER. Effects of S-nitrosohemoglobin (SNO-Hb) on hypoxic pulmonary vasoconstriction (HPV) and nitric oxide flux. American Review of Respiratory and Critical Care Medicine 2001; 163:1164-1170.
10. Cannon III RO, Schechter AN, Panza JA, Ognibene FP, Pease-Fye ME, Waclawiw M, Shelhamer JH, Gladwin MT. Effects of inhaled nitric oxide on regional blood flow are consistent with intravascular nitric oxide delivery. Journal of Clinical Investigation 2001; 108: 279-287.

**The first demonstration that inhaled nitric oxide in humans has systemic vasodilatory and systemic NO signaling effects, and identifies nitrite as the candidate endocrine molecule mediating this effect. Total times cited: 127**

11. Moore DF, Scott LTC, Gladwin MT, Altarescu G, Kaneski C, Suzuki K, Pease-Fye ME, Ferri R, Brady RO, Herscovitch P, Schiffmann R. Regional cerebral hyperperfusion and nitric oxide pathway dysregulation in Fabry disease: reversal by enzyme replacement therapy. Circulation 2001; 104:1506-1512.
12. Gladwin MT, Ognibene FP, Shelhamer JH, Pease-Fye ME, Noguchi CT, Rodgers GP, Schechter AN. Nitric oxide transport on sickle cell hemoglobin: Where does it bind? Free Radical Research 2001; 35:175-180.
13. Zuzak KJ, Schaeberle MD, Gladwin MT, Cannon RO, Levin IW. Noninvasive determination of spatially resolved and time-resolved tissue perfusion in humans during nitric oxide inhibition and inhalation by use of a visible-reflectance hyperspectral imaging technique. Circulation 2001; 104:2905-2910.
14. Alsan M, Ryan TM, Adler B, Townes TM, Parks DA, Thompson AJ, Tousson A, Gladwin MT, Patel RP, Tarpey MM, Batinic-Haberle I, White CR, Freeman BA. Oxygen radical inhibition of

- nitric oxide-dependent vascular function in sickle cell disease. Proceedings of the National Academy of Sciences USA 2001; 98:15215-15220.
15. Noguchi CT, **Gladwin MT**, Diwan B, Merciris P, Smith R, Yu X, Buzard G, Fitzhugh A, Keefer LK, Schechter AN, Mohandas N. Pathophysiology of a sickle cell trait mouse model: human alpha beta-S transgenes with one mouse beta-globin allele. Blood Cells, Molecules, and Diseases 2001; 27:971-977.
  16. **Gladwin MT**, Shelhamer JH, Ognibene FP, Pease-Fye ME, Nichols JS, Link B, Patal DB, Jankowski MA, Pannell LK, Schechter AN, Rodgers GP. Nitric oxide donor properties of hydroxyurea in patients with sickle cell disease. British Journal of Hematology 2002; 116:436-444.
  17. Diwan BA, **Gladwin MT**, Noguchi CT, Ward JM, Fitzhugh AL, Buzard GS. Renal Pathology in Hemizygous Sickle Cell Mice. Toxicology Pathology 2002; 30:254-262
  18. **Gladwin MT**, Wang X, Reiter CD, Yang BK, Vivas EX, Bonaventura C, Schechter AN. S-Nitrosohemoglobin is unstable in the reductive erythrocyte environment and lacks O<sub>2</sub>/NO-linked allosteric function. J Biol Chem. 2002 Aug 2;277(31):27818-28.
  19. Xu X, Lockamy VL, Chen K, Huang Z, Shields H, King SB, Balias SK, Nichols JS, **Gladwin MT**, Noguchi CT, Schechter AN, Kim-Shapiro DB. Effects of Iron Nitrosylation on Sickle Cell Hemoglobin Solubility. Journal of Biological Chemistry 2002; 277:36787-36792.
  20. Huang XL, Pawliczak R, Cowan MJ, **Gladwin MT**, Madara P, Logun C, Shelhamer JH. Epidermal growth factor induces p11 gene and protein expression and down-regulates calcium ionophore-induced arachidonic acid release in human epithelial cells. Journal of Biological Chemistry 2002;277:38431-38440.
  21. Deem S, Kim JU, Manjula BN, Acharya AS, Kerr ME, Patal RP, **Gladwin MT**, Swenson ER. Effects of S-nitrosation and cross-linking of hemoglobin on hypoxic pulmonary vasoconstriction in isolated rat lungs. Circulation Research 2002; 91:626-632.
  22. Reiter CD, Wang X, Tanus-Santos JE, Hogg N, Cannon RO 3rd, Schechter AN, **Gladwin MT**. Cell-free hemoglobin limits nitric oxide bioavailability in sickle cell-disease. Nat Med. 2002 Dec 8(12):1383-9. [Epub 2002 Nov 11.]

**The characterization of a novel mechanism of disease, hemolysis-associated endothelial dysfunction. This work has described a state of resistance to NO in patients with sickle cell disease caused by scavenging of nitric oxide by hemoglobin that is released into plasma during hemolysis. Total times cited: 337**
  23. Nanavaty UB, Pawliczak R, Doniger J, **Gladwin MT**, Cowan MJ, Logun C, Selhamer JH. Oxidant-induced cell death in respiratory epithelial cells is due to DNA damage and loss of ATP. Experimental Lung Research 2002; 28:591-607.

24. Cokic VP, Smith RD, Beleslin-Cokic BB, Njoroge JM, Miller JL, **Gladwin MT**, Schechter AN. Hydroxyurea induces fetal hemoglobin by the nitric oxide-dependent activation of soluble guanylyl cyclase. *The Journal of Clinical Investigation* 2003; 111:231-239.
25. **Gladwin MT**, Schechter AN, Ognibene FP, Coles WA, Reiter CD, Schenke WH, Csako G, Waclawiw MA, Panza JA, Cannon RO 3<sup>rd</sup>. Divergent nitric oxide bioavailability in men and women with sickle cell disease. *Circulation* 2003 Jan;107(2):271-8.
26. Huang X, Pawliczak R, Yao X-L, Cowan MJ, **Gladwin MT**, Walter MJ, Holtzman MJ, Madara P, Logun C, Shelhamer JH. Interferon- $\gamma$  induces p11 gene and protein expression in human epithelial cells through INF- $\gamma$  activated sequences in the p11 promoter. *Journal of Biological Chemistry* 2003; 278:9298-9308.
27. Zuzak KJ, **Gladwin MT**, Cannon RO, Levin IW. Imaging hemoglobin oxygen saturation in sickle cell disease patients using noninvasive visible reflectance hyperspectral techniques: Effects of nitric oxide. *American Journal of Physiology: Heart and Circulatory Physiology* 2003; 285:H1183-H1189.
28. Xu X, Cho M, Spencer NY, Patel N, Huang Z, Shields H, King SB, **Gladwin MT**, Hogg N, Kim-Shapiro DB. Measurements of nitric oxide on the heme iron and  $\beta$ -93 thiol of human hemoglobin during cycles of oxygenation and deoxygenation. *Proceedings of the National Academy of Sciences USA* 2003; 100:11303-11308
29. Cosby K, Partovi KS, Crawford JH, Patel RP, Reiter CD, Martyr S, Yang BK, Waclawiw MA, Zalos G, Xu X, Huang KT, Shields H, Kim-Shapiro DB, Schechter AN, Cannon RO 3<sup>rd</sup>, **Gladwin MT**. Nitrite reduction to nitric oxide by deoxyhemoglobin vasodilates the human circulation. *Nat Med*. 2003 Dec;9(12):1498-505. [Epub 2003 Nov 2.]

**These studies reveal that nitrite is a potent vasodilator in humans and is bioactivated by reaction with deoxyhemoglobin to generate NO preferentially under hypoxic conditions; they also suggest that hemoglobin has an "enzymatic" property as a nitrite reductase that participates in hypoxic vasodilation. Total times cited: 462**

30. Yang BK, Vivas EX, Reiter CD, **Gladwin MT**. Methodologies for the sensitive and specific measurement of S-nitrosothiols, iron-nitrosyls, and nitrite in biological samples. *Free Radic Res.* 2003 Jan;37(1):1-10. Review.
31. **Gladwin MT**, Sachdev V, Jison ML, Shizukuda Y, Plehn JF, Minter K, Brown B, Coles WA, Nichols JS, Ernst I, Hunter LA, Blackwelder W, Schechter AN, Rodgers GP, Castro O, Ognibene FP. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. *N Engl J Med*. 2004 Feb 26;350(9):886-95.

**The mechanistic, clinical, and epidemiological description of a human disease syndrome, hemolysis-associated pulmonary hypertension. Specifically, that pulmonary hypertension occurs in 30% of patients with sickle cell disease, is a major cause of mortality in this**

**population (odds ratio for death of 10:1), and is strongly associated with high hemolytic rate, iron overload, and kidney disease. Total times cited: 308**

32. Jison, ML, Munson PJ, Barb JJ, Suffredini AF, Talwar S, Logun C, Raghavachari N, Beigel JH, Shelhamer JH, Danner RL, and **Gladwin MT**. Blood mononuclear cell gene expression profiles characterize the oxidant, hemolytic, and inflammatory stress of sickle cell disease. Blood 2004; 104:270-280.
33. Wang X, Tanus-Santos JE, Reiter CD, Dejam A, Shiva S, Smith RD, Hogg N, **Gladwin, MT**. Biological activity of nitric oxide in the plasmatic compartment. Proc Natl Acad Sci USA 2004 Aug 3;101(31):11477-82. [Epub 2004 Jul 16.]
34. Deem S, Kim SS, Min JH, Eveland R, Moulding J, Martyr S, Wang X, Swenson ER and **Gladwin MT**. Pulmonary vascular effects of red blood cells containing S-nitrosated hemoglobin. American Journal of Physiology: Heart and Circulatory Physiology 2004 Aug; 287:H2561-H2568.
35. Hunter CJ, Dejam A, Blood AB, Shields H, Kim-Shapiro DB, Machado RF, Tarekgn S, Mulla N, Hooper AO, Schechter AN, Power GG, **Gladwin MT**. Inhaled nebulized nitrite is a hypoxia-sensitive NO-dependent selective pulmonary vasodilator. Nat Med. 2004 Oct;10(10):1122-7. [Epub 2004 Sep 12.]

**The first therapeutic application of sodium nitrite since the application more than 100 years ago as an antidote to cyanide poisoning. Total times cited: 88**

36. Kim-Shapiro DB, **Gladwin MT**, Patel RP, and Hogg N. The reaction between nitrite and hemoglobin: the role of nitrite in hemoglobin-mediated hypoxic vasodilation. Journal of Inorganic Biochemistry 2005; 99:237-247.
37. Hasan S, Elbedawi M, Castro O **Gladwin M**, Palestine A. Central retinal vein occlusion in sickle cell disease. Southern Medical Journal. 2004; 97:202-204.
38. Swenson KE, Eveland RL, **Gladwin MT** and Swenson ER. Nitric oxide (NO) in normal and hypoxic vascular regulation of the spiny dogfish, *Squalus acanthias*. Journal of Experimental Zoology Part A: Comparative Experimental Biology 2005; 303:154-160.
39. Dejam A, Hunter CJ, Pelletier MM, Hsu LL, Machado RF, Shiva S, Power GG, Kelm M, **Gladwin MT**, Schechter AN. Erythrocytes are the major intravascular storage sites of nitrite in human blood. Blood 2005 Jul 15;106(2):734-9. [Epub 2005 Mar 17.]
40. Pluta RM, Dejam A, Grimes G, **Gladwin MT**, Oldfield EH. Nitrite infusions to prevent delayed cerebral vasospasm in a primate model of subarachnoid hemorrhage. JAMA. 2005 Mar 23; 293(12):1477-84.

41. Huang KT, Keszler A, Patel NK, Patel RP, **Gladwin MT**, Kim-Shapiro DB, and Hogg N. The reaction between nitrite and deoxyhemoglobin: Reassessment of reaction kinetics and stoichiometry. *Journal of Biological Chemistry* 2005; 280:31126-31131.

42. Duranski MR, Greer JJ, Dejam A, Jaganmohan S, Hogg N, Langston W, Patel RP, Yet SF, Wang X, Kevil CG, **Gladwin MT**, Lefer DJ. Cytoprotective effects of nitrite during *in vivo* ischemia-reperfusion of the heart and liver. *J Clin Invest*. 2005 May;115(5):1232-40. [Epub 2005 Apr 14.]

**Describes a novel role for nitrite in mediating cytoprotection after ischemia-reperfusion injury.** These studies have lead to the current hypothesis that dietary nitrate, via salivary reduction to nitrite, may represent the active cardioprotective ingredient in the Mediterranean diet. This study paved the way for more than 30 other original research studies showing nitrite-mediated cytoprotection of the brain, liver, kidney, heart and lung. Total times cited: 189

43. Morris CR, Kato GJ, Poljakovic M, Wang X, Blackwelder WC, Sachdev V, Hazen ST, Vichinsky EP, Morris SM Jr. and **Gladwin MT**. Dysregulated arginine metabolism, hemolysis-associated pulmonary hypertension and mortality in sickle cell disease. *Journal of the American Medical Association* 2005; 294:81-90.

**Expands on the mechanism of hemolysis-mediated endothelial dysfunction by identifying a critical role for red blood cell arginase 1, that catabolizes L-arginine when released into plasma during red cell hemolysis.** Total times cited: 160

44. Huang Z, Shiva S, Kim-Shapiro DB, Patel RP, Ringwood LA, Irby CE, Huang KT, Ho C, Schechter AN, Hogg N, and **Gladwin MT**. Enzymatic function of hemoglobin as a nitrite reductase that produces nitric oxide under allosteric control. *J Clin Invest*. 2005 Aug;115(8):2099-107. [Epub 2005 Jul 21.]

**Describes a novel chemical reaction pathway, R-state catalysis (also referred to as R-state auto-catalysis).** From a physiological perspective this study reveals that hemoglobin is an allosterically regulated nitrite reductase that generates nitric oxide maximally when partially deoxygenated (around the P<sub>S0</sub>). This finding links NO generation to hypoxic sensing in hemoglobin and provides the first evidence that other hemoproteins are likely to function as nitrite reductases. Total times cited: 140

45. Machado RF, Martyr S, Kato GJ, Barst RJ, Anthi A, Robinson MR, Hunter L, Coles W, Nichols J, Hunter C, Sachdev V, Castro O, **Gladwin MT**. Sildenafil therapy in patients with sickle cell disease and pulmonary hypertension. *Br J of Haematol*. 2005 Aug;130(3):445-53.

46. Kato GJ, Martyr S, Blackwelder WC, Nichols J, Coles W, Hunter L, Hazen SL, and **Gladwin MT**. Levels of soluble endothelium-derived adhesion molecules in patients with sickle cell disease are associated with haemolytic rate, multi-organ failure, and risk of death. *British Journal of Haematology* 2005; 130:943-953.

47. Piknova B, **Gladwin MT**, Schechter AN and Hogg N. Electron paramagnetic resonance analysis of nitrosylhemoglobin in humans during NO inhalation. *Journal of Biological Chemistry* 2005; 280:40583-40588.
48. Azarov I, Huang KT, Basu S, **Gladwin MT**, Hogg N and Kim-Shapiro DB. Nitric oxide scavenging by red blood cells as a function of hematocrit and oxygenation. *Journal of Biological Chemistry* 2005; 280:39024-39032.
49. Minneci PC, Deans KJ, Zhi H, Yuen P, Star RA, Banks SM, Schechter AN, Natanson C, **Gladwin MT** and Solomon SB. Hemolysis-associated endothelial dysfunction mediated by accelerated NO inactivation by decompartmentalized oxyhemoglobin. *Journal of Clinical Investigation* 2005; 115:3409-3417.
50. Crawford JH, Isbell TS, Huang Z, Shiva S, Chacko BK, Schechter AN, Darley-Usmar VM, Kerby JD, Lang Jr JD, Kraus D, Ho C, **Gladwin MT**, and Patel RP. Hypoxia, red blood cells and nitrite regulate NO-dependent hypoxic vasodilatation. *Blood* 2006; 107:566-574.
51. Kato GJ, McGowan VR, Machado RF, Little JA, Taylor J 6th, Morris CR, Nichols JS, Wang X, Poljakovic M, Morris SM Jr , and **Gladwin, MT**. Lactate dehydrogenase as a biomarker of hemolysis-associated nitric oxide resistance, priapism, leg ulceration, pulmonary hypertension and death in patients with sickle cell disease. *Blood* 2006 Mar 15;107(6):2279-85. [Epub 2005 Nov 15.]
52. Hataishi R, Rodrigues AC, Neilan TG, Morgan JG, Buys E, Shiva S, Tambouret R, Jassal DS, Raher MJ, Furutani E, Ichinos F, **Gladwin MT**, Rosenzweig A, Zapol WM, Picard MH, Bloch KD, and Scherrer-Crosbie M. Inhaled nitric oxide decreases infarction size and improves left ventricular function in a murine model of myocardial ischemia-reperfusion injury. *American Journal of Physiology: Heart and Circulatory Physiology* 2006; 291:H379-384.
53. Grubb JR, Dejam A, Voell J, Blackwelder WC, Sklar PA, Kovacs JA, Cannon RO, Masur H, **Gladwin MT**. Lopinavir-ritonavir: effects on endothelial cell function in healthy subjects. *J Infect Dis.* 2006 Jun 1; 193(11):1516-9. [Epub 2006 Apr 27.]
54. Kato GJ, Hsieh M, Machado R, Taylor J 6<sup>th</sup>, Little J, Burman JA, Lehky T, Tisdale J, and **Gladwin MT**. Cerebrovascular disease associated with sickle cell pulmonary hypertension. *American Journal of Hematology* 2006; 81:503-510.
55. Holly MK, Dear JW, Hu X, Schechter AN, **Gladwin MT**, Hewitt SB, Yuen PS and Star RA. Biomarker and drug-target discovery using proteomics in a new rat model of sepsis-induced acute renal failure. *Kidney International* 2006; 70:496-506.
56. Machado RF, Anthi A, Steinberg MH, Bonds D, Sachdev V, Kato GJ, Taveira-DaSilva AM, Ballas SK, Blackwelder W, Xu X, Hunter L, Barton B, Waclawiw M, Castro O, **Gladwin MT**;

- MSH Investigators. N-terminal pro-brain natriuretic peptide levels and risk of death in sickle cell disease. *Journal of American Medical Association* 2006; 296(3):310-318.
57. Wang X, Bryan NS, MacArthur PH, Rodriguez J, **Gladwin MT**, Feelisch M. Measurement of NO levels in the red cell: validation of tri-iodide-based chemiluminescence with acid-sulfanilamide pretreatment. *J of Biol Chem*. 2006 Sep 15;281(37):26994-7002. [Epub 2006 Jul 14.]
56. Shiva S, Wang X, Ringwood LA, Xu X, Yuditskaya S, AnnavaJJhala V, Miyajima H, Hoog N, Harris ZL, **Gladwin MT**. Ceruloplasmin is a NO oxidase and nitrite synthase that determines endocrine NO hemostasis. *Nat Chem Biol*. 2006 Sep; 2(9):486-483. [Epub 2006 Aug 13.]
- First demonstration that ceruloplasmin has alternative function as an NO oxidase and nitrite synthase. Total times cited: 64**
58. Little JA, McGowan VR, Kato GJ, Partovi KS, Feld JJ, Maric I, Martyr S, Taylor JG 6<sup>th</sup>, Machado RF, Heller T, Castro O, **Gladwin MT**. Combination erythropoietin-hydroxyurea therapy in sickle cell disease: experience from the National Institutes of Health and a literature review. *Haematologica*. 2006 Aug; 91(8):1076-83.
59. Dias-Junior CA, **Gladwin MT** and Tanus-Santos JE. Low-dose intravenous nitrite improves hemodynamics in a canine model of acute pulmonary thromboembolism. *Free Radical Biology and Medicine* 2006; 14:1764-1770.
60. Jeffers A, **Gladwin MT**, Shapiro DB. Computation of plasma hemoglobin nitric oxide scavenging in hemolytic anemias. *Free Radical Biology and Medicine* 2006; 41:1557-1565.
61. Hsu LL, Champion HC, Campbell-Lee SA, Bivalacqua TJ, Manci EA, Diwan BA, Schimel DM, Cochard AE, Wang X, Schechter AN, Noguchi CT and **Gladwin MT**. Hemolysis in sickle cell mice causes pulmonary hypertension due to global impairment in nitric oxide bioavailability. *Blood*. 2007; 109:3088-3098.
62. Machado, RF, Mack AK, Martyr S, Barnett C, MacArthur P, Sachdev V, Ernst I, Hunter LA, Coles WA, Nichols JP, Kato GJ and **Gladwin MT**. Severity of pulmonary hypertension during vaso-occlusive pain crisis and exercise in patients with sickle cell disease. *Br J Haematol*. 2007 Jan;136(2):319-25. [Epub 2006 Dec 8.]
63. Sachdev V, Machado RF, Shizukuda Y, Rao YN, Sidenko S, Ernst I, St. Peter M, Coles WA, Rosing DR, Blackwelder WC, Castro O, Kato GJ, **Gladwin MT**. Diastolic dysfunction is an independent risk factor for death in patients with sickle cell disease. *Journal of the American College of Cardiology* 2007; 49:472-479.
64. Shiva S, Huang Z, Grubina R, Sun J, Ringwood LA, MacArthur PH, Xu X, Murphy E, Darley-Usmar VM, **Gladwin MT**. Deoxymyoglobin is a nitrite reductase that generates nitric oxide

and regulates mitochondrial respiration. *Circ Res*. 2007 Mar 16;100:654-61. [Epub 2007 Feb 9.]

**The first demonstration that myoglobin has a physiological function as a nitrite reductase that generates NO in the heart during hypoxia. These studies have now been confirmed in the myoglobin knock out mouse and new studies reveal a role for myoglobin mediated nitrite reduction in myocardial energetics and in hypoxic vasodilation. Total times cited: 110**

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56. Lundberg JO, Weitzberg E, and **Gladwin MT**. The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics. *Nature Reviews Drug Discovery* 2008; 7:156-167.
57. **Gladwin MT** and Kim-Shapiro DB. The functional nitrite reductase activity of the heme-globins. *Blood* 2008 Jul 2.
58. **Gladwin MT**, Patel RP. The role of red blood cells and hemoglobin-nitric oxide interactions on blood flow. *Am J Respir Cell Mol Biol* 2008 Feb;38(2):125-6.
59. **Gladwin MT**. Evidence mounts that nitrite contributes to hypoxic vasodilation in the human circulation. *Circulation* 2008 Feb 5;117(5):594-7.
60. Wood KC, Hsu LL, **Gladwin MT**. Sickle cell disease vasculopathy: a state of nitric oxide resistance. *Free Radic Biol Med* 2008 Apr 15;44(8):1506-28.
61. Krajewski ML, Hsu LL, **Gladwin MT**. The proverbial chicken or the egg? Dissection of the role of cell-free hemoglobin versus reactive oxygen species in sickle cell pathophysiology. *Am J Physiol Heart Circ Physiol* 2008 Jul;295(1):H4-7.
62. **Gladwin MT**, Grubina R, Doyle MP. The new chemical biology of nitrite reactions with hemoglobin: R-state catalysis, oxidative denitrosylation, and nitrite reductase/anhydrase. *Acc Chem Res* 2009 Jan 20;42(1):157-67. Review.
63. Kettenhofen NJ, Wang X, **Gladwin MT**, Hogg, N. In-gel detection of S-nitrosated protein using fluorescence methods. *Methods Enzymol*. 2008; 441:53-71.
64. Sinha SS, Shiva S, **Gladwin MT**. Myocardial protection by nitrite: evidence that this reperfusion therapeutic will not be lost in translation. *Trends Cardiovasc Med*. 2008 Jul;18(5):163-72.

65. Morris CR, **Gladwin MT**, Kato GJ. Nitric oxide and arginine dysregulation: a novel pathway to pulmonary hypertension in hemolytic disorders. *Curr Mol Med*. 2008 Nov; 8(7):620-32.
66. Basu S, Wang X, **Gladwin MT**, Kim-Shapiro DB. Chemiluminescent detection of S-nitrosated proteins: comparison of tri-iodide, Copper/CO/cysteine, and modified copper/cysteine methods. *Methods Enzymol*. 2008; 440:137-56.
67. Shiva S, **Gladwin MT**. Shining a light on tissue NO stores: near infrared release of NO from nitrite and nitrosylated hemes. *J Mol Cell Cardiol*. 2009 Jan; 46(1):1-3.
68. Kato GJ, **Gladwin MT**. Evolution of novel small-molecule therapeutics targeting sickle cell vasculopathy. *JAMA*. 2008 Dec 10;300(22):2638-46.
69. **Gladwin MT**, Vichinsky E. Pulmonary complications of sickle cell disease. *N Engl J Med*. 2008 Nov 20;359(21):2254-65.
70. **Gladwin MT**. Current and future therapies of sickle cell anemia: an historical perspective *Hematology AM Soc Hematol Educ Program*. 2008:176.
71. van Faassen EE, Bahrami S, Feelisch M, Hogg N, Kelm M, Kim-Shapiro DB, Kozlov AV, Li H, Lundberg JO, Mason R, Nohl H, Rassaf T, Samoilov A, Slama-Schwok A, Shiva S, Vanin AF, Weitzberg E, Zweier J, **Gladwin MT**. Nitrate as regulator of hypoxic signaling in mammalian physiology. *Med Res Rev*. 2009 Sep; 29(5):683-741.
72. Shiva S, **Gladwin MT**. Nitrite mediates cytoprotection after ischemia/reperfusion by modulating mitochondrial function. *Basic Res Cardiol*. 2009 Mar;104(2):113-9.
73. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, Elliott CG, Gaine SP, **Gladwin MT**, Jing ZC, Krowka MG, Langleben D, Nakanishi N, Souza R. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2009 Jun 30;54(1 Suppl):S43-54.
74. **Gladwin MT**, Kim-Shapiro DB. Storage lesion in banked blood due to hemolysis-dependent disruption of nitric oxide homeostasis. *Curr Opin Hematol*. 2009 Nov;16(6):515-23.
75. Raat NJ, Shiva S, **Gladwin MT**. Effects of nitrite on modulating ROS generation following ischemia and reperfusion. *Adv Drug Deliv Rev*. 2009 Apr 28;61(4):339-50.
76. **Gladwin MT**, Shiva S. The ligand binding battle t cytochrome c oxidase: how NO regulates oxygen gradients in tissue. *Circ Res*. 2009 May 22;104(10):1136-8.
77. Williams KM, Chien JW, **Gladwin MT**, Pavletic SZ. Bronchiolitis obliterans after allogeneic hematopoietic stem cell transplantation. *JAMA*. 2009 Jul 15;302(3):306-14.

78. Kato GJ, Hebbel RP, Steinberg MH, **Gladwin MT**. Vasculopathy in sickle cell disease: Biology, pathophysiology, genetics, translational medicine, and new research directions. *Am J Hematol*. 2009 Sept;84(9):618-25.
79. Lundberg JO, **Gladwin MT**, Ahluwalia A, Benjamin N, Bryan NS, Butler A, Cabrales P, Fago A, Feelisch M, Ford PC, Freeman BA, Frenneaux M, Friedman J, Kelm M, Kevil CG, Kim-Shapiro DB, Kozlov AV, Lancaster JR Jr, Lefer DJ, McColl K, McCurry K, Patel RP, Petersson J, Rassaf T, Reutov VP, Richter-Addo GB, Schechter A, Shiva S, Tsuchiya K, van Faassen EE, Webb AJ, Zuckerbraun BS, Zweier JL, Weitzberg E. Nitrate and nitrite in biology, nutrition and therapeutics. *Nat Chem Biol*. 2009 Dec;5(12):865-9.
80. Donadee CL, **Gladwin MT**. Hemodialysis hyperhemolysis a novel mechanism of endothelial dysfunction and cardiovascular risk? *J Am Coll Cardiol*. 2010 Feb 2;55(5):460-2.
81. Lee JS, **Gladwin MT**. Bad blood: the risks of red cell storage. *Nat Med*. 2010 Apr;16(4): 381-2.
82. **Gladwin, MT**, Ghofrani HA. Update on pulmonary hypertension 2009. *Am J Respir Crit Care Med*. 2010 May 15;181(10):1020-6.
83. Machado RF, **Gladwin MT**. Pulmonary hypertension in hemolytic disorders: pulmonary vascular disease: the global perspective. *Chest*. 2010 Jun;137(6 Suppl):30S-38S.
84. **Gladwin MT**, Barst RJ, Castro OL, Gordeuk VR, Hillery CA, Kato GJ, Kim-Shapiro DB, Machado R, Morris CR, Steinberg MH, Vichinsky EP. Pulmonary hypertension and NO in sickle cell. *Blood*. 2010 Aug 5;116(5):852-4.
85. Jain S, **Gladwin MT**. Arginine metabolism and nitric oxide bioavailability in sickle cell disease. *J Pediatr Hematol Oncol*. 2010 Oct;32(7):3247-8.

## **CHAPTERS**

1. Copeland JR, **Gladwin MT**, and Shelhamer JH. Therapeutic TARgets of Airway Inflammation. N. T. Eissa and D. P. Huston, eds. New York: Marcel Decker. 2003. Nitric Oxide, reactive nitrogen species and lipid mediator generation in the lung. .
2. Kato GJ and **Gladwin MT**. Principles of Critical Care, Third Edition. Hall JB and Schmidt GA, eds., New York: McGraw-Hill, 2005, Sickle Cell Disease. pp 1655-1670.
3. Machado RF and **Gladwin MT**. Pulmonary Vascular Disease. J. Mandell and D. Taichman, eds., first edition, Philadelphia, PA: Saunders Elesvier. 2006. Hemolytic Anemia Associated Pulmonary Hypertension. pp 170-187
4. Dezfulian C, **Gladwin MT**, and Shiva S. Nitric Oxide. B Tota and B Trimmer, eds. The Netherlands: Elsevier. 2007. Nitrite is a vascular store of NO which mediates hypoxic signaling and protects against ischemia/reperfusion injury. , pp 213-227.

5. Shiva S and **Gladwin MT**. Endothelial Biomedicine. W Aird, eds. Cambridge, New York: University Press. 2007. Cross-talk between the red blood cell and the endothelium: Nitric oxide as a paracrine and endocrine regulator of vascular tone. , pp 562-575.
6. Kato GJ and **Gladwin MT**. Disorders of Hemoglobin: Genetics, Pathophysiology, Clinical Management-2nd Steinberg MH, Forget BG, Higgs D, Nagel RL. ed., in press. Mechanisms of Hemolysis in Sickle Cell Disease and Thalassemia.
7. Morris, CR, **Gladwin MT**. Pulmonary Circulation Diseases and Their Treatments. 3<sup>rd</sup> edition: Chapter XX. Peacock AJ, Naeije R, Rubin L ed. Hemolysis-Associated Pulmonary Hypertension in Sickle Cell Disease and Thalassemia.
8. Klings, ES, **Gladwin, MT**. Textbook of Pulmonary Vascular Disease. New York, NY:Springer Science and Business Media, Inc; 2009. Yuan, JX-J, Garcia, J, Hales, CA, Archer SL, Rich, S, West, JB ed. Hemolytic anemia associated pulmonary hypertension (Sickle cell disease and Thalassemia-Associated PH).
9. Machado, RF, **Gladwin, MT**. Textbook of Respiratory Medicine. 5<sup>th</sup> ed. Vol. II Philadelphia: Saunders; 2010. Mason, RJ, Broaddus VC; Martin TR, King, TE Jr, Schraufnagel DE, Murray JR, Nadel JA. ed. Pulmonary Complications of Hematologic Diseases. Chapter 84.

#### **BOOKS:**

**Clinical Microbiology Made Ridiculously Simple** has been most popular textbook of microbiology in medical schools since 1997, selling approximately 20,000 copies each year in the US and internationally. The book is the highest rated in "First AID for the Boards" and has been translated into Spanish, Portuguese, Japanese and Chinese.

1. **Gladwin MT**, Trattler W. Clinical Microbiology Made Ridiculously Simple. 1st ed. Miami (FL): Medmaster, Inc; 1995.
2. **Gladwin MT**, Trattler W. Clinical Microbiology Made Ridiculously Simple. 2nd ed. Miami (FL): Medmaster, Inc; 1997.
3. **Gladwin MT**, Trattler W. Clinical Microbiology Made Ridiculously Simple. 3rd ed. Miami (FL): Medmaster, Inc; 2001.
4. **Gladwin MT**, Trattler W. Clinical Microbiology Made Ridiculously Simple. 4th ed. Miami (FL): Medmaster, Inc; 2007.

#### **TRAINEES:**

<b><u>Pre IRTAs</u></b>	<b><u>Dates</u></b>	<b><u>Trainee</u></b>	<b><u>Current Position</u></b>
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2001 - 2002	Ester Vivas	Med Student, Albert Einstein Univ Sch of Med
2001 - 2002	Benjamin Yang	Med Student, George Washington Univ Med Sch
2003 - 2004	Cynthia Irby	Med Student, UAB Medical School
2003 - 2004	Salem Tarekgn	Med Student, Univ of Chicago Medical School
2002 - 2004	Sabrina Martyr	Med Student, Howard University Medical School
2004 - 2005	Vidya Annavajjhala	Med Student, Texas Tech
2003 - 2005	Zhi (James) Huang	Med Student, Univ of Maryland School of Medicine
2004 - 2005	Mildred Pelletier	Student, University of Alabama at Birmingham
2002 - 2005	Kristine Partovi	Data Manager, California
2004 - 2006	Lorna Ringwood	Graduate Sch -Biomedical Engineering, VA Tech
2004 - 2006	Amy Harris	Master's in Public Health Program, GW University
2004 - 2006	Vicki McGowan	Med School - Edward Via VA College of Osteopathic Medicine, Blacksburg, VA
2005 - 2006	Laura Kirby	Lab Technician, Loma Linda University, CA
2005 - 2006	Veronica Vasquez	Med School, Univ of Washington, Seattle, WA
2005 - 2007	Peter MacArthur	Med Student, Univ of Maryland School of Medicine
2006 - 2007	Aleksey Alekseyenko	Master's Program, Univ of Boston, Boston, MA
2006 - 2007	Erin Curtis	Academic Counselor, UC Irvine, CA
2006 - 2008	Eleni Footman	Medical School, Howard University Medical School, Washington, DC
2006 - 2008	Virginia Liu	Medical School, University of Southern California, Irvine, CA

#### CRTPs

<u>Dates</u>	<u>Trainee</u>
2000 - 2001	Karin Minter
2003 - 2005	Christian Hunter
2004 - 2005	Susan Yuditskaya
2004 - 2005	Elaina Lin
2005 - 2006	Adam Berg
2005 - 2006	Ashaunta Tumblin
2006 - 2007	Candice Bereal

#### Howard Hughes

<u>Dates</u>	<u>Trainee</u>
2006 - 2007	Rozalina Grubina

#### Post Doctoral Fellows

<u>Dates</u>	<u>Trainee</u>
2001 - 2004	Christopher Reiter, Ph.D.
2003 - 2005	Andre Dejam, M.D.,Ph.D.
2006 - 2008	Geng Liu, Ph.D.
2004 - 2008	Struti Shiva, Ph.D.
2006-2010	Harold Raat, Ph.D.

#### Current Position

Pediatric Resident, Duke University
Residency at Harvard, Boston, MA
Medical School, Univ of Pittsburgh Medical School
Med School, John Hopkins Univ Sch of Medicine
Med Student, George Washington Medical School
Medical Student, Harvard Medical School
Medical Student, UCLA, CA

#### Current Position

Med Student, John Hopkins Univ Sch of Medicine

#### Current Position

R 21 award – 2009 - Research Scientist, Biochemistry GenVec, Inc
Cardiology Fellow, Beth Israel, Boston, MA
University of Pennsylvania, PA
RO1 funded - Assistant Professor, University of Pittsburgh, Pittsburgh, PA
Henry Jackson Foundation Grant, 2008 –

		Assistant Professor, Department of (Experimental) Anesthesiology, Erasmus Medical Center, Rotterdam, The Netherlands
2006 - 2008	Katherine Wood, Ph.D.	Postdoctoral fellow, NHLBI, NIH
2007 - 2008	Mauro Tiso, Ph.D.	Postdoctoral fellow, University of Maryland Pittsburgh, PA
2009-Present	Ling Wang, M.D, Ph.D.	Postdoctoral Associate, Vascular Medicine Institute (VMI), University of Pittsburgh, Pittsburgh, PA
2009-Present	-Jun Wang, Ph.D.	Postdoctoral Associate, Vascular Medicine Institute (VMI), University of Pittsburgh, Pittsburgh, PA

### **Senior Fellows**

<b><u>Dates</u></b>	<b><u>Trainee</u></b>	<b><u>Current Position</u></b>
1999 - 2004	Maria Jison, M.D.	Physician, Mid Atlantic Pulmonary Clinic, Kensington, MD
2003 - 2005	Peter Minneci, M.D.	K23 award - Assistant Professor, Children's Hospital of Philadelphia, Philadelphia, PA (CHOP)
2003 – 2005	Kate Deans, M.D.	Assistant Professor, Children's Hospital of Philadelphia, Philadelphia, PA (CHOP)
2003 - 2006	A. Kyle Mack, M.D.	Assistant Professor, Children's Memorial Hospital, Chicago, IL
2003 - 2006	Jose Villagra, M.D.	K12 award - Staff Physician, Children's National Medical Center, Washington, DC
2005 - 2007	Zakari Aliu, M.D.	Hematologist, Assistant Professor, Howard University Hospital, Washington, DC
2006 - 2008	Cameron Dezfulian, M.D.	K23 funded – Assistant Professor, University of Miami, Miami, FL
2006 - 2008	Jacqueline Janka, M.D.	Fellow, Critical Care Medicine Department, CC, NIH
2007 – 2008	Michael Cuttica, M.D.	K12 award – Assistant Professor, Northwestern University, Chicago, IL
2007 – 2008	Hans Ackerman, M.D.	Intramural Research Funds 2009 - Critical Care Medicine Department, NIAID
2009-Present	Chenelle Donadee, M.D.	Fellow, Gladwin Lab (Gladwin VMI Grant)
2009-Present	Jason Stamm, M.D.	Fellow, Gladwin Lab (Gladwin VMI Grant)

### **Faculty**

<b><u>Dates</u></b>	<b><u>Trainee</u></b>	<b><u>Current Position</u></b>
2003 - 2004	Roberto Machado, M.D.	K12 award – Assistant Professor, University of Chicago, Chicago, IL
2003 - 2008	Lewis L. Hsu, M.D.	Contract Scientist, NIH
2003-2006	Jose Villagra, M.D.	Staff Physician, Children's National Medical Center, Washington, DC
2005-Present	Gregory Kato, M.D.	Intramural Research Funds, 2008 - Section Chief,

	Tenure Track, NHLBI, NIH
2006-Present James Taylor, M.D.	Intramural Research Funds - Staff Clinician, Intramural Research Division, NHLBI, NIH
2009-Present Jeffrey Isenberg, MD, MPH	K22 award, 2008 – Research Assistant Professor of Medicine, University of Pittsburgh, Pittsburgh, PA
2009-Present Enrico Novelli, MD	Assistant Professor of Medicine, Hematology/Oncology, Director Adult Sickle Cell Anemia Program, Associate Director, Hemophilia Center of Western PA

### Current INDs Held

Hydroxyurea, L-arginine, Sildenafil (Viagra) 67,143	
L-NMMA	69,068
Oxypurinol	69,069
Acetylcholine	69,070
Sodium Nitrite	70,411
Carbon Monoxide	70,694
Nitric Oxide	74,053
Revatio™ (Sildenafil) Capsules	77,461
Erythropoientin and Hydroxyurea	100,068

### PATENTS:

1. Co-inventor on “USE OF NITRITE SALTS FOR THE TREATMENT OF CARDIOVASCULAR CONDITIONS”, filed as International application number: PCT/US2004/022232, (published as WO2005/004884 ) PCT/US2004/021985, (published as WO/2005/007173

This patent has been licensed to Hope Pharmaceuticals, who have completed phase I human studies and are now conducting three phase II trials in subarachnoid aneurismal hemorrhage to prevent vasospasm, sickle cell disease and myocardial infarction.

A second license for inhaled nitrite has been awarded to Aires Pharmaceuticals who have completed animal toxicology studies, phase I human trials and phase Ib human trials. Novartis has now partnered with Aires for Phase II development. Phase II trials are set to begin in 2011.

2. Co-inventor on “NITRITE-METHEMOGLOBIN THERAPY TO DETOXIFY STROMA-FREE HEMOGLOBIN BASED BLOOD SUBSTITUTES”, filed as provisional patent E-259-2007 0-US-01; 4239-79173-01; US No 60/969,530 U.S. Provisional Application No. 60/996,530 filed 31 Aug 2007 PCT/US2008/074856 (published as WO2009/029836)
3. Co-inventor on “METHODS OF TREATMENT FOR HEMOLYSIS”, filed as a provisional patent WFU ref. number 08-10. PCT/US2008/010950
4. Co-inventor on “FIVE-COORDINATE NEUROGLOBIN AND USE THEREOF AS A BLOOD SUBSTITUTE”, filed as US utility application from the University of Pittsburgh; Application number 8123-83317-02 US app 12/817,085 filed June 16, 2010. 01942

Co-inventor on "NEUROGLOBIN AS A SIX-TO-FIVE COORDINATE REGULATED NITRITE REDUCTASE". Provisional application 61/187527 filed June 16, 2009. University Pittsburgh 01942/US application

### **PROFESSIONAL ACTIVITIES**

- Founder and Director of the Unity Health Care Asthma/Pulmonary Clinic  
Mission: 1) Deliver pulmonary subspecialty care to the homeless and indigent patients at the 2<sup>nd</sup> and E Street and Cardoza clinics and 2) Establish contacts between minority patients and NIH clinical research protocols (supported by the Office for Research in Minority Health, NIH, and the Critical Care Medicine Department, CC, NIH)
- Attending Physician at the Howard University Comprehensive Sickle Cell Anemia Center.
- Scientific Liaison to the Board of Directors for the National Organization for Wellness of Children and Families with Sickle Cell Disease, Inc. (NOW-CFSCD)
- Scientific Liaison to the Board of Directors for the Spring off Life Wellness Center in Prince George's County, Maryland
- NIH – Grant Reviewer: Ad Hoc RC1, RC2, RC4, MIM study section
- NHLBI – Advisory subcommittee – Pulmonary/Cardiac Disease
- American Society for Clinical Investigation – Elected to Council – 2010
- Clinical and Translational Science Institute (CTSI) Advisory Board - July, 2008-present -
- PACCm Fellowship committee - July, 2008- present –
- Vascular Medicine Institute – Director - Advisory Board - October, 2008-present
- NHLBI subcommittee – Cardiac and Pulmonary Disease in Sickle Cell Anemia to guild NHLBI in their Restructuring of the SCD Research Enterprise - September, 2008-present
- Pennsylvania Department of Health, Health Research Advisory Committee, Harrisburg, PA. Public Testimony - October 24, 2008
- ASCI – Council Meeting – November 11-13, 2010

### **AD HOC MANUSCRIPT PEER REVIEWER**

American Journal of Respiratory and Critical Care Medicine  
Blood  
British Journal of Hematology  
Circulation  
Circulation Research  
Free Radical Biology and Medicine  
Journal of the American Medical Association  
Journal of Clinical Investigation  
Journal of Experimental Medicine  
Nature  
Nature Chemical Biology

Nature Medicine  
New England Journal of Medicine  
Proceedings of the National Academy of Sciences  
Science  
Science Translational Medicine

#### **EDITORIAL BOARD MEMBER**

Haematologica (2008-2010)  
Journal of Hematology (Approved 2007)  
Free Radical Biology and Medicine (Approved 2007)  
Pulmonary Circulation (Approved 2010)  
American Journal of Respiratory and Critical Care Medicine (invited for 2011)

#### **CHAIRED SESSIONS**

November 9, 2003 – American Heart Association in Orlando, FL: Sickle Cell Vasculopathy: New insights

November 20, 2003 – Society of Free Radical Biology and Medicine in Seattle, WA: Methods in Free Radical Biology and Medicine and their Applications to Translational Research

December 6-9, 2008 - Chairperson of an Education Program Session at the 2008 American Society of Hematology meeting in San Francisco, California entitled “Current and Future Therapies in Sickle Cell Anemia”

February 4, 2010 – Session Chair – Department of Medicine Faculty Research Retreat, Pittsburgh, PA. Developing Multiple PI Grants.

#### **MEETINGS ORGANIZED**

March 17-18, 2004 – First International Nitrite “Tie” Meeting. Bethesda, Maryland

September 8- 9, 2005 – Role of nitrite in Physiology, Pathophysiology and Therapeutics Meeting. Bethesda, Maryland

December 7-8, 2006 – Evolution of Pulmonary Hypertension: Emerging Diseases and Novel Therapeutics Meeting. Bethesda, Maryland

September 6-7, 2007 - Second International Role of Nitrite in Physiology, Pathophysiology and Therapeutics. Bethesda, Maryland

October 9-10, 2009 – Pittsburgh International Lung Conference – Spotlight on Pulmonary Hypertension and Pulmonary Vascular Biology. University of Pittsburgh, Pittsburgh, PA

**INVITED LECTURES**

March 1993. American College of Physicians Winning and Finalist Abstract, 74th Annual Session, Washington, D.C.

June 1995. Grand Rounds, Oregon Health Sciences University, Portland, OR.

March 1999. Plenary Presentation, National Sickle Cell Disease Program, San Francisco, CA.

July 1999. Johns Hopkins University EPR Research Center, Baltimore, MD.

September 1999. Grand Rounds, Clinical Center, National Institutes of Health, Bethesda, MD.

October 1999. Cardiology Branch, NHLBI, National Institutes of Health, Bethesda, MD.

February 2000. Grand Rounds, Oregon Health Sciences University, Portland, OR.

March 2000. Howard University Anesthesiology Dept, Washington DC.

April 2000. Cardiology Branch, NHLBI, National Institutes of Health, Bethesda, MD.

June 2000. Plenary Presentation, 1<sup>st</sup> Annual Nitric Oxide Society Meetings, San Francisco, CA. Relative role of heme nitrosylation and -cysteine 93 nitrosation in the transport and metabolism of nitric oxide by hemoglobin in the human circulation.

August 30-31, 2000. Presented at the Center for Free Radical Biology Meeting at the University of Alabama at Birmingham: Role of nitrite and SNO-hemoglobin in the regulation of blood flow in man.

September 5-6, 2000. Presented at the NHLBI extramural workshop: Nitric oxide as a Therapeutic Agent in Sickle Cell Disease.

September 20, 2000. Presented plans for pulmonary hypertension trial at the Annual Sickle Cell Disease Clinical Research Meetings, Natcher Conference Center, NIH

October 23, 2000. Presented at the American College of Chest Physicians Meeting, San Francisco, CA. Nitric oxide in the Pathophysiology and Treatment of the Acute Chest Syndrome of Sickle Cell Anemia.

October 30, 2000. Presented at a symposium in honor of the Benesches, held at the Caspary Auditorium of Rockefeller Institute, New York City. Hemoglobin Structure and Oxygen-nitric Oxide Delivery (Organized by Franklin Bunn).

November 14, 2000. Presented at the American Heart Association Scientific Sessions, New Orleans, LA. Role of Circulating Nitrite and S-Nitrosohemoglobin in Regulating Regional Vascular Flow in Man.

December 4, 2000. Presented at the American Society of Hematology Meetings, San Francisco, CA. Nitric Oxide Donor Properties of Hydroxyurea.

January 17, 2001. NIH Clinical Center Grand Rounds. NO Therapy in Sickle Cell Disease.

February 4-8, 2001. Presented at the Gordon Research Conference on Nitric Oxide Biochemistry and Biology, Ventura, CA. NO Reactions with Hemoglobin.

2001. Presented at the Research Symposium on Nitric Oxide Reactions with Hemoglobin. FASEB meetings, Orlando, FL.

August 16, 2001. Presented at Georgetown University Grand Rounds. Pulmonary Complications of Sickle Cell Anemia: Role of Nitric Oxide Therapy.

February 2002. Presented at Johns Hopkins University Grand Rounds. Role of Nitric Oxide in the Pathophysiology and Therapy of Sickle Cell Anemia.

April 18, 2002. Presented at the Medical College of Wisconsin Free Radical Research Center. Nitric Oxide Reactions with Hemoglobin in the Human Circulation.

May 13, 2002. Presented at Columbia University Renal Grand Rounds. Nitric Oxide Reactions with Hemoglobin Plasma Proteins in the Human Circulation.

September 12, 2002. Presented at the AARC Conference by the Sea 2002. Ocean City, Maryland. Nitric Oxide – Back to the Future.

September 21, 2002. Presented at the Sickle Cell Disease Association of America 30<sup>th</sup> Annual Convention, Washington, D.C. Pulmonary Complications of Sickle Cell Disease

November 6, 2002. Presented at CHEST 2002, San Diego, CA. Role of Nitric Oxide in the Pathophysiology and Treatment of Sickle Cell Disease.

November 21, 2002. Presented at the 9<sup>th</sup> Annual Meeting of the Oxygen Society, San Antonio, TX. Nitric Oxide Therapy in Sickle Cell Disease.

December 4, 2002. Presented at the Hematology Fellowship Conference, National Institutes of Health, Bethesda, MD. Nitric Oxide, Hemolysis, and Sickle Cell Disease.

December 7, 2002. Presented at the American Society of Hematology Meeting, Philadelphia, PA. A Prospective Clinical Study of the Prevalence and Etiology of Secondary Pulmonary Hypertension in Sickle Cell Anemia.

January 9, 2003. Presented to the Surgeon General, Vice Admiral Richard H. Carmona, Bethesda, MD. Sickle Cell Research Program at the Clinical Center, National Institutes of Health.

January 21, 2003. Presented at Children's Hospital of Philadelphia, Philadelphia, PA. Pulmonary Complications of Sickle Cell Disease: Role of NO in Pathogenesis and Treatment.

February 19, 2003. Presented at University of Minnesota, Minneapolis, MN. Pulmonary Complications of Sickle Cell Disease: Nitric Oxide in the Pathogenesis and Therapy of Sickle Cell Disease.

March 14, 2003. Presented at New York University School of Medicine, New York, NY. Pulmonary Complications of Sickle Cell Anemia: Role of NO in Pathogenesis and Treatment.

April 30, 2003. Presented at Wake Forest University, Winston-Salem, NC. Role of Nitric Oxide in the Pathogenesis and Therapy of Sickle Cell Disease.

May 7, 2003. Presented at Cleveland Clinic Foundation, Cleveland, OH. Role of Nitric Oxide in the Pathogenesis and Therapy of Sickle Cell Disease.

May 20, 2003. Presented at the American Thoracic Society Meeting, Seattle, WA. Pediatric Clinical Chest Rounds.

October 13, 2003. Presented at the Clinical Center 50<sup>th</sup> Anniversary Scientific Symposium, Bethesda, MD. Recruitment of Minorities in Research.

October 25, 2003. Presented at the 90<sup>th</sup> Meeting of the Red Cell Club, Yale University School of Medicine, New Haven, CT. Novel Function of Hemoglobin as a Nitrite Reductase Regulates Hypoxic Vasodilation.

November 9, 2003. Presented at the American Heart Association Meeting, Orlando, FL. Oxidative Stress in Sickle Cell Disease.

November 20, 2003. Presented at the Society of Free Radical Biology and Medicine Meeting, Seattle, WA.

December 6, 2003. Presented at the American Society of Hematology Meeting, San Diego, CA. Scientific Committee on Hemoglobin/Red Cell: Hemoglobin and Oxygen Homeostasis: Nitric Oxide-Hemoglobin Reactions in Sickle Cell Disease Pathogenesis.

December 11, 2003. Presented at Health Sciences Center School of Medicine, Shreveport, LA. NO-hemoglobin Reactions in Health and Disease.

January 8, 2004. Presented at University of Alabama at Birmingham, AL. Nitric Oxide and Sickle Cell Disease.

January 29, 2004. Presented at the Tri-State Chest Physician's Conference at the University of

Pittsburgh, Pittsburgh, PA. Unraveling the Reactions of Nitric Oxide, Nitrite and Hemoglobin in the Regulation of Human Blood Flow.

January 30, 2004. Presented Pulmonary Grand Rounds at the University of Pittsburgh, Pittsburgh, PA. Role of Nitric Oxide in the Pathogenesis and Treatment of Sickle Cell Disease.

February 13, 2004. Presented at the Research Conference of the Division of Pulmonary and Critical Care Medicine at the University of Florida in Gainesville, FL. Unraveling the Reactions of Nitric Oxide, Nitrite and Hemoglobin in the Human Physiology Pathophysiology.

March 4, 2004. Presented at the Pulmonary Hypertension in the 21<sup>st</sup> Century: The Beginning of a New Era Course at Johns Hopkins University School of Medicine, Baltimore, MD. Emerging Causes of Pulmonary Hypertension II: Sickle Cell Disease.

May 13, 2004. Presented at the UK Forum on Haemoglobin Disorders at King's College Hospital in London England. Emerging Causes of Pulmonary Hypertension: Sickle Cell Disease and Hemolysis-Associated Pulmonary Hypertension.

May 14, 2004. Presented at the University College in London, England. Sickle Cell Disease and Hemolysis-Associated Pulmonary Hypertension.

June 7, 2004. Presented at the Sickle Cell Disease Advisory Committee meeting at the National Institutes of Health, Bethesda, MD.

June 12, 2004. Presented at the International PAH Experts Conference in New York City, NY. Sickle Cell Disease and Other Hemolytic Anemia - A Newly Recognized Cause of PAH.

June 17, 2004. Presented at the Oxygen Club of Greater Washington, D.C. Unraveling the Reactions of Nitrite and Hemoglobin in Human Physiology and Therapeutics.

September 23, 2004. Presented at the Twenty-Third Annual Symposium Immunohematology & Blood Transfusion at the National Institutes of Health, Bethesda, MD. Emerging Causes of Pulmonary Hypertension: Sickle Cell Disease and Hemolysis-Associated Pulmonary Hypertension.

October 5, 2004. Presented at the Molecular Medicine of Infection and Inflammation, Common Pathways, Pediatric Rare Diseases Meeting, Bethesda, MD. Mechanisms of Hemolysis-Associated Endothelial Dysfunction and Pulmonary Hypertension.

October 23, 2004. Presented at the American Association of Blood Banks Meeting, Baltimore, MD. Unraveling the Reactions of Nitric Oxide, Nitrite and Hemoglobin in Human Physiology and Therapeutics.

November 7, 2004. Presented at the CME-Certified Satellite Symposium at the American Heart Association Meeting, New Orleans, LA. Sickle Cell Disease and Hemolysis-Associated Pulmonary Hypertension.

January 25, 2005. Presented at Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA. Unraveling the Reactions of Nitric Oxide, Nitrite and Hemoglobin in Human Physiology and Therapeutics.

January 26, 2005. Presented Cardiology Grand Rounds, Boston MA. Emerging Causes of Pulmonary Hypertension: Hemolysis-associated Endothelial Dysfunction.

February 3, 2005. Presented at the Western Section American Federation for Medical Research, Western Society for Clinical Investigations, Western Association of Physicians, Carmel, CA. Role of NO in the Pathogenesis and Therapy of Sickle Cell Disease.

February 22-27, 2005. Presented at the Hypoxia Meeting, Lake Louise, Canada. Red Cells and NO Transport in Vasoregulation

March 15, 2005. Presented at the GRC Conference on Oxidative Stress and Disease, Ventura Beach, CA. Unraveling the Reactions to NO, Nitrite and Hemoglobin in Physiology and Therapeutics.

March 19, 2005. Presented at the Eighth Cooley's Anemia Symposium, Lake Buena Vista, FL. The pathologic Changes Caused by Hemolysis Induced NO Deficiency in Thalassemia.

March 24, 2005. Presented Grand Rounds at Children's Hospital, Pittsburgh, PA. Emerging Causes of Pulmonary Hypertension: Hemolysis-associated Endothelial Dysfunction.

April 14-15, 2005. Presented at the Sanquin Spring Seminar in, Amsterdam, The Netherlands. RBC Metabolism, Including the Role of NO - Unraveling the Reactions to NO, Nitrite and Hemoglobin in Physiology and Therapeutics.

April 28, 2005. Presented Grand Rounds at Columbia-Presbyterian Medical Center in New York City, New York. Sickle Cell Disease and Pulmonary Hypertension.

May 22-27, 2005. Presented at the GRC Conference on Nitric Oxide, Il Ciocco, Barga, Italy. Unraveling the Reactions to NO, Nitrite and Hemoglobin in Physiology and Therapeutics.

July 21, 2005. Presented at the BioScience 2005 Conference in Glasgow, England. Nitric Oxide Signaling – New Targets, New Biochemistry. Unraveling the Reactions to NO, Nitrite and Hemoglobin in Physiology and Therapeutics.

October 6-7, 2005. Presented at the Cellular and Molecular Mechanisms or Right Heart Failure Working Group in Bethesda, MD. Nitrite based therapeutics for cardiac ischemic-reperfusion injury and pulmonary hypertension.

October 18, 2005. Presented at the NIH Research Festival, Bethesda, MD. Plenary Session: Unraveling the Reactions of Nitric Oxide, Nitrite and Hemoglobin in Human Physiology and Therapeutics.

December 10-13, 2005. Presented at the American Society of Hematology meeting in Atlanta, GA. Cardiopulmonary Complications: Role of NO and Hemolytic Anemia.

December 10-13, 2005. Presented a Plenary Session at the American Society of Hematology meeting in Atlanta, GA. Brain Natriuretic Peptide Identifies Pulmonary Hypertension as Major Risk for Death in MSH Trial in 1996.

January 6-11, 2006. Presented at the 35<sup>th</sup> Critical Care Congress in San Francisco, CA. Effect of Nitrite Derived NO on Tissue Injury.

March 23-25, 2006. Presented at the Society of French Hematology annual meeting in Paris, France. NO and No2 of Hemoglobin and Hoe do Erythrocytes Induce Vasodilatation?

April 1-6, 2006. Presented at the FASEB Meeting in San Francisco, CA. Nitrite Anion as a Biological Nitric Oxide Donor.

April 4, 2006. Presented Grand Rounds at San Francisco General Hospital. Hemolysis Associated Endothelial Dysfunction and Pulmonary Hypertension: Emerging Cause of Death in Patients with Hemoglobinopathies.

April 6, 2006. Presented Grand Rounds at University of California, San Francisco. Hemolysis Associated Endothelial Dysfunction and Pulmonary Hypertension: Emerging Cause of Death in Patients with Hemoglobinopathies.

April 10-11, 2006. Presented a Plenary Session, Roland Scott Lecture at the National Sickle Cell Disease Program annual meeting in Memphis, TN. Hemolysis-associated Endothelial Dysfunction and Pulmonary Hypertension: An Emerging Cause of Death in Sickle Cell Disease.

April 22, 2006. Presented at the Pharmacotherapy Frontiers 2006 Meeting at the NIH in Bethesda, MD. Nitrite Therapeutics: Back to the Future.

May 19, 2006. Presented at the Cardiovascular Symposium at the University of Alabama at Birmingham, AL. Role of Nitrite in Hypoxic Signaling and Therapeutics.

June 23, 2006. Presented at Children's Hospital Oakland Research Institute Symposium, Oakland, CA. Unraveling the Reactions of Nitric Oxide, Nitrite, and Hemoglobin in Human Physiology and Therapeutics.

June 25-29, 2006. Presented at the Nitric Oxide Society Fourth International Conference on Biology, Chemistry and Therapeutic Applications of Nitric Oxide in Monterey CA. Emerging Biology of Nitrite in Signaling Hypoxic Vasodilation in Cytoprotection.

September 18, 2006. Presented Grand Rounds at Johns Hopkins School of Medicine, Baltimore, MD. Hemolysis Associated Endothelial Dysfunction and Pulmonary Hypertension in Sickle Cell Disease.

October 7-10, 2006. Presented at the Europaediatrics 2006 Congress in Barcelona, Spain. NO and Hemoglobin in the Microcirculation Control.

October 21-26, 2006. Presented at the American College of CHEST Physicians meeting in Salt Lake City, Utah. Emerging Approaches to Pulmonary Complications of Sickle Cell Disease and Other Hemolytic Anemias.

November 14, 2006. Presented at the Functional Genomics Symposium, National Institutes of Health, Bethesda, MD. Nitrite as an Intrinsic Signaling Molecule that Regulates Hypoxic NO Homeostasis and Cytoprotection.

November 17, 2006. Presented Medical Grand Rounds at Johns Hopkins School of Medicine, Baltimore, MD. Hemolysis associated pulmonary hypertension: an emerging cause of death in patients with hemoglobinopathies.

November 17, 2006. Presented at the Lung Research Seminar at Johns Hopkins School of Medicine, Baltimore, MD. Unraveling the reactions of nitrite, nitric oxide and hemoglobin in physiology and therapeutics.

December 8, 2006. Presented at the Evolution of Pulmonary Hypertension: Emerging Diseases and Novel Therapeutics Meeting, NIH, Bethesda, MD. Therapy with Nitrite.

February 4-9, 2007. Presented at the 7<sup>th</sup> Nitric Oxide Gordon Research Conference in Ventura Beach, CA. Nitrite Regulation of Regional Blood Flow Control.

March 30 – April 5, 2007. Presented at the Society for Experimental Biology Conference in Glasgow, Scotland. Integrated Red Blood Cell Functions.

April 12, 2007. Presented at the 2006-2007 Evans Medicine Research Seminar Series, Boston, MA. Unraveling the Reactions of Nitrite and Hemoglobin in Physiology and Therapeutics.

April 18, 2007. Presented at the 21<sup>st</sup> Annual Comprehensive Update and Board Review for Critical Care Medicine, McLean, VA. Pulmonary Hypertension: Management in the ICU.

May 15 – 20, 2007. Presented at the 7<sup>th</sup> Annual Scientific Meeting of the NO Society of Japan in Otsu, Japan. Unraveling the Reactions of Nitrite and Hemoglobin in Physiology and Therapeutics. Hemolysis Associated Endothelial Dysfunction: An Emerging Cause of Pulmonary Hypertension and Death.

June 1, 2007. Presented at the Nobel Forum, Karolinska Institutet as part of the series “Frontiers in Biomedical Research”, Stockholm, Sweden.

June 14 - 15, 2007. Presented at the 2007 Health Care for the Homeless Conference, Washington, DC. Clinical Update: Asthma and COPD Management for the Primary Care Provider.

September 12, 2007. Presented Grand Rounds at Washington VA Medical Center, Washington, D.C.

September 25 – 26, 2007. Presented at the University Hospital of the Rheinisch Westfälische Technische Hochschule in Aachen, Germany. Role of Nitrite in Myocardial and Vascular Diseases.

September 27, 2007. Presented at the Excellence Cluster Cardio-Pulmonary System in Bad Nauheim, Germany. Emerging Biology of Nitrite in Signaling Hypoxic Vasodilation and Therapeutic Cytoprotection.

October 16, 2007. Presented at the Capri Science Conference in Capri, Italy. Nitrite/Nitric Oxide Pathway in Physiology and Therapeutics.

November 14-18, 2007. Presented at the Society of Free Radical Biology and Medicine Meeting in Washington, DC.

December 3-4, 2007. Presented at Weill Cornell Medical College in New York, NY. The Nitrite-NO Pathway in Physiology and Therapeutics.

February 3 – 8, 2008. Presented at the 2008 Oxygen Radicals in Biology Gordon Research Conference, Ventura, CA. Nitrite Chemistry and Nitrite Signaling.

February 11-14, 2008. Presented at the 4<sup>th</sup> World Symposium on Pulmonary Hypertension. Dana Point, Orange County, CA. Task Force/Working Group Member – Basic Science, Classification and Epidemiology.

February 20, 2007. Presented Grand Rounds at the NIH, Bethesda, MD. Nitric Oxide and Sickle Cell Vasculopathy Mechanism of Disease and novel Therapeutic Strategies.

February 28 – March 2, 2008. Presented at the Clinical State-of-the-Art Course (SOTA XIII) for ATS, in Chicago, IL. Pulmonary and ICU Complications of Sickle Hemoglobinopathies.

April 2 – April 4, 2008. Gave the Abelson Lecture at St. Louis, MO. Hemolysis-associated endothelial dysfunction and pulmonary hypertension: An emerging cause of death in sickle cell disease.

April 30, 2008. Presented at the HBOC Workshop, Lister Hill Auditorium, National Institutes of Health, Bethesda, MD. Can we harness the nitrite reductase/anhydrase activity of the heme globins to offset NO scavenging base toxicity?

April 30 – May 4, 2008. Presented Grand Rounds in Seattle, WA. The Nitrite-Nitric Oxide Pathway in Physiology and Therapies and Hemolysis-associated endothelial dysfunction and pulmonary hypertension: An emerging cause of death in sickle cell disease.

May 5 – 7, 2008. Presented Grand Rounds at the University of California, San Diego, CA. The Nitrite-Nitric Oxide Pathway in Physiology and Therapies and Hemolysis-associated endothelial dysfunction and pulmonary hypertension: An emerging cause of death in sickle cell disease.

May 22 – 25, 2008. Presented at the Nemacolin Meeting in Pittsburgh, PA. Heme globins as functional nitrite reductase.

May 26 – 29, 2008. Presented at the Sanquin Research Meeting in Amsterdam, Netherlands. The Nitrite-Nitric Oxide Pathway in Physiology and Therapies.

May 30, 2008. Presented at the DHHS Advisory Committee Meeting on Blood Safety and Availability in Rockville, MD. NO Binding.

June 6, 2008. Presented at the Yale Symposium in Boston MA. The Hemoglobinopathies and Pulmonary Hypertension.

June 26, 2008. Presented at the NMRC Navy Conference I Silver Spring, MD. No-Hb chemistry, interactions, and rationale for amelioration of HBOC vasoactivity.

August 30-September 2, 2008 - Invited speaker. Damage Associated Molecular Pattern Molecules (DAMPs) and Alarmins Symposium, Pittsburgh, PA.

September 12, 2008. Presented at Nitrite Meeting – NHLBI, Bethesda, MD. Proposed RCT of LDM in the Prevention of Recurrent MI, Stroke, and CV Death Among ACS Patients with Persistent Elevatin of C-Reactive Protein.

October 2, 2008. Presented at the University of Pittsburgh Science 2008, Pittsburgh, PA. Haldane, Hot Dogs, and Halitosis: The Emerging Biology of Nitrite Anion.

October 5-7, 2008. Organizing Committee/Presented at the Mitochondrial Biology in Cardiovascular Health and Diseases Conference, Natcher Conference Center, NIH, Bethesda, MD.

October 22-24, 2008. Co-Chair, Sickle Cell Disease Workshop: Clinical Priorities and Clinical Trials, NIH, Bethesda, MD.

December 6-9, 2008. Presented at the 50<sup>th</sup> American Society of Hematology (ASH) Meeting and Exposition, San Francisco, CA. Haldane, Hotdogs, and Halitosis: The Emerging Biology of the Anion Nitrite.

January 12, 2009 – Presented at the University of Iowa, Iowa City, IA. Visiting Professor. Nitrite-NO Pathway: Physiology and Therapeutics.

January 31-Feb 4, 2009-Invited speaker, Critical Care Congress, Nashville, TN.

February 1-3, 2009 – Presented Plenary Lecture at the 38<sup>th</sup> Critical Care Congress, 2009 Society of Critical Care Medicine Meeting. Nashville, TN. Haldane, Hot Dogs and Halitosis: The Emerging Biology of the Nitrite Anion in Physiology and Therapeutics.

February 5-8, 2009 – Presented at the 2009 ATS State of the Art Course (SOTA XIV), Chicago, IL. Complications of Sickle Hemoglobinopathies

February 13, 2009 – Presented at the University of Pittsburgh Medical Grand Rounds, Pittsburgh, PA. Hemolysis Associate Pulmonary Hypertension: An Emerging Cause of Death in Hemolytic Diseases

February 20-22, 2009 – Presented at the University of Pittsburgh Winter Academy, Naples, FL. Haldane, Hot Dogs, and Halitosis: Nitrite in Health and Disease.

February 25, 2009 – Facilitator for MSTP course, Research Basis of Medical Knowledge (MSTP 5290). University of Pittsburgh and Carnegie Mellon University.

February 27, 2009 - Speaker, Adult Sickle Cell Program, Pittsburgh, PA. Advances in Sickle Cell.

March 1-6, 2009 – Presented at the NO Gordon Research Conference, Lucca (Barga), Italy. Discussion Leader – Dietary Sources of Nitrite and Cardiovascular Function: Keeping up the NO

March 12, 2009 - Invited speaker, Gilead, San Francisco, CA.

March 22-26, 2009 - Invited speaker, ACS, Salt Lake City, Utah. Presented Coordination Chemistry of Nitric Oxide and its Implication for Metabolism Imaging and Toxicity.

April 3-7, 2009- Invited speaker - Critical Care Medicine 2009, Mclean, Virginia. Pulmonary Hypertension: Management in the ICU.

April 16-18, 2009 - Invited speaker, Gulf Coast Physiology Society Meeting, New Orleans, LA. Haldane, Hot Dogs and Halitosis: the Emerging Biology of the Nitrite Anion in Cardiovascular Physiology.

May 12, 2009 – Invited speaker, Molecular Medicine Research Seminar, Children's Hospital of Pittsburgh, Haldane, Hot Dogs and Halitosis: The Emerging Biology and Therapeutic Application of Nitrite

May 13, 2009 - Invited speaker, Hematology Oncology Grand Rounds, Pittsburgh, PA. New Research Institute and Research on Sickle Cell.

May 12-14, 2009 - Invited speaker, Neonatal and Childhood and Pulmonary Vascular Disease, San Francisco, CA. Pulmonary Arterial Hypertension and Sickle Cell Disease.

May 15-19 2009 - Invited speaker, ATS Conference, San Diego, CA. The Interplay of Hemolysis, Redox Biology and Dysregulated Nitric Oxide Metabolism in PH of SCD.

May 27, 2009 – Invited speaker, Magee Women's Research Institute Work-in-Progress (WIP) Seminar Series, Pittsburgh, PA. Haldane, Hot Dogs and Halitosis: The Emerging Biology and Therapeutic Application of Nitrite.

May 28, 2009-Invited speaker, Grand Rounds, Children's Hospital, Pittsburgh, PA.

June 12-26, 2009 - Invited speaker, Presented at the Third International Meeting on the Role of Nitrite in Physiology, Pathophysiology and Therapeutics, on Nitrite on Reduction by Five and Six Coordinated Heme Globins. Karolinska Institute.

September 10-12, 2009 - Invited speaker, Sleep and Breathing Symposium, Pittsburgh, PA.: NO and nitrites/nitrates.

September 13-15, 2009 - Invited speaker. Hemophilia Center of Western PA, Pittsburgh, PA.

September 17-18, 2009 - Invited speaker, Redox Signaling and Disease Symposium. University of Michigan.

October 9-10, 2009 - Invited speaker, Pittsburgh International Lung Conference. Vascular Biology and Pulmonary Hypertension. Pittsburgh, PA.

October 23, 2009 - Invited speaker, UPMC Discovery Day, Pittsburgh, PA.

October 28-30, 2009 - Invited speaker, Sickle Cell Disease - Inflammation, Thrombosis, and Vascular Injury Working Group, Bethesda, MD. Vascular Injury.

October 29, 2009 - Invited speaker, Walter Reed Army Institute of Research

November 14-18, 2009 - Invited speaker, American Heart Association, Orlando, FL. Prevalence and Pathobiology of Pulmonary Hypertension in Sickle Cell Disease.

November 20-22 2009 - Invited speaker, Pulmonary Hypertension Summit 2009, Cleveland Clinic. Nitrite Therapeutics.

November 23, 2009 - Invited speaker, Novartis Pharmaceutical Meeting, Pittsburgh, PA. Research on COPD, Asthma, Pulmonary Hypertension and Pulmonary Fibrosis.

December 4, 2009 - Invited speaker: Mini Symposium: The Heme Globin Family as Functional Nitrite Reductases and NO-signaling Molecules, Duquesne University.

December 5-8, 2009 - Invited speaker, ASH Conference, New Orleans, LA.

December 15, 2009 - Hartwell Foundation Interview. Neuroglobin and nitrite therapy for sickle cell stroke. Pittsburgh, PA.

December 17, 2009 - Invited Speaker. Presented at the Public Health Implications of Sickle Cell Trait Key Opinion Leader Meeting, Atlanta, GA.

January 8-13, 2010-Invited speaker, Critical Care Congress, Miami, FL.

January 13-14, 2010- Invited speaker, Albert Einstein College of Medicine and Montefiore Medical Center, New York City. Hemolysis-associated endothelial dysfunction and pulmonary hypertension: An emerging cause of death in the hemolytic anemias".

January 25-27, 2010 - University of Pittsburgh Fellows Research Retreat. Seven Springs Mountain Resort, Seven Springs, PA.

February 2-3, 2010 - Invited Speaker. NIH Study Session,. Melrose Hotel, Washington DC.

February 17-18, 2010 - Invited Review Panel Member. Howard Hughes Medical Institute, Chevy Chase, MD.

March 7-9, 2010 - Invited Speaker. National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, MD.

March 11-12, 2010 - Invited Speaker. University of Pennsylvania School of Medicine. Hot dogs, Haladane, and Halitosis: The Role of Nitrite Anion in the Hypoxic Signaling and Therapeutics. Philadelphia, PA.

March 23, 2010 - External Advisory Board Speaker. Vascular Medicine Institute, Department of Medicine, University of Pittsburgh, Pittsburgh, PA.

April 8-9, 2010 - Invited Speaker - University of Texas Institute of Molecular Medicine. Haldane, Hot Dogs and Halitosis: The Emerging Biology and Therapeutic Application of Nitrite. Houston, TX.

May 4-5, 2010- Oxidase and Cell Signaling Conference, University of Pittsburgh, Pittsburgh, PA

May 19, 2010- Invited Speaker - NIH Scientific Management Review Board, Panel Presentation: Expanding the Use of the NIH Clinical Center: Potential Opportunities and Collaborations. Bethesda, MD.

May 27-29, 2010 – Invited Speaker – Wake Forest Nitrogen Oxide Meeting (NOX-3). Reactions of Nitrite with Neuroglobin. Nemacolin Resort, Farmington, PA

June 14-18 2010 - Invited Speaker 6<sup>th</sup> International Conference on the Biology, Chemistry, and Therapeutic Applications of Nitric Oxide. Role of Nitrite in Hypoxic Signaling and Therapeutics. Kyoto, Japan.

June 21, 2010 – Fenwal – Invited speaker – Scientific Advisory Board Meeting. Red Cell Storage RO-1. Chicago, IL

July 15-16, 2010 – Invited Speaker – Gilead Sciences, Inc. PAH Medical Affairs Advisory Program. Screening for pulmonary hypertension in at risk patient populations. Foster City, CA

September 5-8, 2010 – Invited Speaker – Bayer Schering Research Center. Hemoysis mediated endothelial dysfunction and therapeutic potential of sGC activators. Duesseldorf, Germany.

September 25, 2010—Invited Speaker—8<sup>th</sup> Annual International Symposium on Transfusion Immunology and Related Topics: Red Blood Cell Storage Lesions and Related Transfusion Issues. Nitric Oxide and Stored Blood. University of Toronto, Toronto, Canada.

October 7, 2010—Invited Speaker—Harvard Lung Conference, Lung Injury and Vascular Injury II. Hypoxic Signaling and Therapeutics in Pulmonary Arterial Hypertension, Harvard University. Boston, MA.

October 7-8, 2010—Invited Speaker—Science 2010 Transformations, Curing Disease: The Role of the Nitrite Anion in Hypoxic Signaling and Cytoprotection. University of Pittsburgh, Pittsburgh, PA.

October 15, 2010 – Invited Speaker – NHLBI Sickle Cell Disease Advisory Committee. Hypothesis that NO scavenging by cell-free plasma hemoglobin contributes to endothelial dysfunction and sickle cell. National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD.

October 25, 2010 – Invited Speaker – Fourth Annual Ri.MED Scientific Symposium – New Drugs, New Vaccines and New Insights into the Cause and Prevention of Human Diseases. Hemolysis associated pulmonary hypertension and end organ failure: a major cause of death in sickle cell disease and thalassemia. Villa Igia, Palermo, Italy.

November 11-14, 2010. The American Society for Clinical Investigation – 2010 Fall Council Meeting. Santa Barbara, CA.

November 17-21, 2010 – Invited Speaker – 17<sup>th</sup> Annual Meeting Society of Free Radical Biology and Medicine (SFRBM) and Society for Free Radical Research International (SFRRI). Recent Insights into the Biological Signaling Properties of Sodium Nitrite. Orlando, FL.

#### **TEACHING:**

Adjunct Clinical Faculty in the School of Nursing, Family Nurse Practitioner Program—Duquesne University School of Nursing, 2008-2009.

Ad hoc medical school lectures

Attending in MICU 6 weeks a year, training on rounds

#### **RESEARCH:**

##### **1. Current Research Grant**

##### **ACTIVE**

<b>Role</b>	<b>Dates</b>	<b>Agency</b>	<b>Title</b>	<b>Annual DC</b>
PI	2/19/09-	Henry M.	Multifunctional Blood Substitute (MBS) for	\$336,589

	9/19/11	Jackson Foundation/ ARMY	Field Resuscitation of Polytrauma Combat Casualties with Brain Injury and Concomitant Hemorrhagic Shock	
PI	9/18/2009-7/31/2013	NHLBI 1 R01 HL098032-01	Storage Lesion in Banked Blood Due to Disruption of Nitric Oxide Hemostasis	\$502,253
Co-PI	04/01/2010-03/31/2015	NIH 1 R01 HL096973-01A1	Myoglobin as a Nitrate Reductase that Regulates Hypoxic Cardiac NO Signaling	\$269,589
Co-PI	9/30/2009-9/29/2011	NIDDK 1 RC1 DK085852-01	Dietary Nitrate Activation of PPARgamma Improves Insulin Sensitivity	\$329,762
Co-I	9/30/2009-08/31/2011	NHLBI RC2 HL101212-01	Genetic Diversity of Sickle Cell Anemia	\$143,849
Co-I	9/9/2009-9/8/2011	NCRR	University of Pittsburgh Clinical and Translational Science Institute (CTSI)	\$244,189
PI	7/1/2008-6/30/2013	Institute for Transfusion Medicine	Vascular Medicine Institute (Admin. Core)	\$262,306
Co-I	8/15/2009-5/31/2014	NHLBI 1 R01 HL 095973-01A1	Role of Nitrate and Hemoglobin in Vascular NO Homeostasis in the Fetus and Adult	\$37,240
PI	7/1/2008-6/30/2013	Institute for Transfusion Medicine	Vascular Medicine Institute-Gladwin	\$1,388,889
PI	9/1/2010-8/31/2012	Bayer Corporation	The Use of sGC Activators to Bypass Nitric Oxide Scavenging by Hemolysis in Sickle Cell Disease	\$40,000
PI	07/01/2008-06/30/2013	Hemophilia Center of Western PA	Vascular Medicine Institute-Shiva	\$1,250,000
PI	09/23/2009-09/22/2011	NIAMS 1 P30 AR058910-01	Translational Vascular Biology in Autoimmune Diseases	\$499,858
PI	12/01/08-10/31/10	Children's Hospital of Pittsburgh	Phase II/III Trial of Sildenafil for Sickle Cell Disease Associate Pulmonary Hypertension-Clinical Sites	\$98,806

PENDING

Role	Dates	Agency	Title	Annual DC
PI	04/01/2011-03/31/2016	NIH 1 P01 HL103455-	Vascular Subphenotypes of Lung Disease	\$1,674,326

		01A1		
Co-PI	4/01/11-3/31/2016	NIH 1 R01 HL103660-01	Mechanisms of Red Cell Transfusion Associated Lung Inflammatory Injury	\$250,000
Co-I	12/01/2010-11/30/2011	NIH	Biomarkers of Cardiopulmonary Disease and Mortality in Sickle Cell Disease	\$293,290
Co-I	12/01/2010-11/30/2013	DOD	Small molecule, gas based therapies to prevent organ injury from trauma/hemorrhage	\$6,356
PI	07/01/2011-06/30/2014	NIH	Nitric Oxide Synthase Recoupling in Pulmonary Arterial Hypertension	\$154,582

#### PRIOR

PI	01/01/2009-12/15/2009 (NCE Pending)	INO Therapeutics	A Prospective Multicenter, Double Blind, Randomized, Placebo-Controlled Study of Nitric Oxide for Inhalational in the Acute Treatment of Sickle Cell Plain Crisis	\$65,016
Co-investigator	7/1/08-6/30/10	NIH	Treatment of Pulmonary Hypertension and Sickle Cell Disease with Sildenafil Therapy	\$226,331
Co-investigator	03/01/2009-03/31/2010	New England Medical Center	Data Coordinating for the Sickle Cell Disease Clinical Research Network	\$2,586

#### 2. Prior Intramural Research Grant Support

1999: Bench to Bedside Award (\$85,000), from the Director of the NIH and the Director of the NIH Clinical Center, for research with nitric oxide therapeutics in sickle cell anemia.

2000: Fare Travel Award; ATS Travel Award.

2000: CRADA with INO Therapeutics Inc. CRADA will cover up to \$500,000 over 3 years for the Pulmonary Hypertension in Sickle Cell Disease-Inhaled NO project.

2000: \$250,000 from the National Center on Minority Health and Health Disparities, National Institutes of Health for support of the Nitric Oxide / Sickle Cell Anemia project.

2001: Two year Bench to Bedside Award (\$75,000), from the Director of the NIH and the Director of the NIH Clinical Center, for a new protocol "Targeted Delivery of Nitric Oxide by Hemoglobin to Improve Regional Blood Flow in Sickle Cell Disease".

2001: ATS Travel Award.

2001: Academic Medicine Mentor Award (\$8,000) awarded by the Fellowship Program in Academic Medicine for Minority Students (sponsored by Bristol-Myers Squibb Co) for the mentorship of Karin R. Mintor.

2002: \$200,000 per year for 3 years from the National Center on Minority Health and Health Disparities, National Institutes of Health

2003: \$150,000 per year for 5 years from the National Heart Lung and Blood Institute, National Institutes of Health for cardio-pulmonary evaluation of the MSH patients

2004: \$99,500 per year for 2 years from the Office of Rare Diseases, National Heart Lung and Blood Institute, and the Clinical Center for Therapeutic Application of Intravascular Nitrite for Sickle Cell Disease.

2005: CRADA with INO Therapeutics Inc. CRADA will cover up to \$376,000 per year over 3 years for the Pulmonary Hypertension in Sickle Cell Disease-Inhaled NO project and the DeNOVO protocol.

2005: Secured NHLBI funding for an 11 million dollar 4-year multicenter study (RFP mechanism) of sildenafil for sickle cell disease associated pulmonary hypertension; Secured estimated 1.5 million in active drug and placebo from Pfizer.

2006: Clinical Trials Agreement with Actelion for ASSET 1 and 2 Trial; \$200,000 per year.

2006: Two year Bench to Bedside Award (\$100,000), from the Director of the NIH and the Director of the NIH Clinical Center, for a new protocol "Hemolysis, HIV/AIDS and Parasitic Infections Associated Secondary Pulmonary Arterial Hypertension in Sickle Cell Diseases".

2006: Two year Bench to Bedside Award (\$100,000), from the Director of the NIH and the Director of the NIH Clinical Center, for a new protocol "Pilot Trial of Intravenous Nitrite for Sickle Cell Vaso-Occlusive Pain Crisis".

2007: Two year Bench to Bedside Award (\$100,000 per year), from the Office of Rare Diseases, and the National Heart Lung and Blood Institute for "Antiproliferative Therapy for severe Pulmonary Arterial Hypertension".

2007: Two year Bench to Bedside Award (\$100,000 per year) from the National Center on Minority Health and Health Disparities, National Institutes of Health, National Heart Lung and Blood Institute, and the Clinical Center for "Contribution of Stromal Free Hemoglobin, Red Cell Membranes, and Red Cell Lysateon Nitric Oxide Inactivation in the Chronic Hemolytic State".

2007: 5 year contract for NIH/INOVA Advanced Lung Disease Center (\$550,000 per year) from the National Heart Lung and Blood Institute, National Institutes of Health.

## CURRENT RESEARCH PROTOCOLS

## Human Protocols

Principal Investigator, NIH Clinical Protocol #01-CC-0078: **Targeted Delivery of Nitric Oxide by Hemoglobin to Improve Regional Blood Flow in Sickle Cell Disease** – Completed 12/02

Principal Investigator; NIH Clinical Protocol #98-CC-0129: **Physiologic Effects of Inhaled Nitric Oxide, Nitroglycerin, and Placebo in Patients with Sickle Cell Anemia** – Completed 7/03

Associate Investigator; NIH Clinical Protocol #97-H-0061: **Evaluation and Treatment of Pulmonary Patients not Participating in Research.**

Associate Investigator; NIH Clinical Protocol # 00-H-0031: **Vascular Effects of Endothelium-Derived Versus Hemoglobin-Transported Nitric Oxide in Healthy Subjects.**

Principal Investigator; NIH Clinical Protocol #01-DK-0088: **Determining the Prevalence and Prognosis of Secondary Pulmonary Hypertension in Adults with Sickle Cell Anemia.**

Principal Investigator; NIH Clinical Protocol #01-H-0223: **Inhaled Nitric Oxide for the Therapy of Patients with Sickle Cell Anemia and Secondary Pulmonary Hypertension.** Open for analysis only.

Associate Investigator; NIH Clinical Protocol # 01-H-0140: **Nitric Oxide Inhalation Therapy for Myocardial Ischemia in Patients with Coronary Artery Disease.**

Principal Investigator; NIH Clinical Protocol #03-CC-0015: **Collection of Blood from Volunteers and Patients for Studies of Endothelial Function and Systemic Inflammation.**

Associate Investigator; NIH Clinical Protocol #03-H-0020: **Determination of Nitrite as a Source of Bioactive Nitric Oxide in Human Subjects.** – Completed 12/03

Principal Investigator, NIH Clinical Protocol #03-CC-0127: **Evaluation of Potential Synergy of Combining Hydroxyurea with Nitric Oxide Donors on Fetal Hemoglobin Synthesis in Patients with Sickle Cell Anemia.** Open for analysis only.

Accountable Investigator and Associate Investigator: NIH Clinical Protocol #04-CC-0032: **Atorvastatin Therapy in Therapy to Improve Endothelial Function in Sickle Cell Disease.** Open for analysis only.

Accountable Investigator and Associate Investigator: NIH Clinical Protocol #04-CC-0085: **The Effect of Lopinavir/Ritonavir Therapy on Endothelial Function in Normal Volunteers -** Completed 9/05

Accountable Investigator and Associate Investigator: NIH Clinical Protocol #04-H-0161: **Studies of the Natural History of Sickle Cell Disease and Other Hemolytic Disorders.**

**Associate Investigator: NIH Clinical Protocol #05-CC-0012: Effects of Inhaled Carbon Monoxide on Pulmonary Inflammatory Responses Following Endotoxin Instillation.**

**Associate Investigator: NIH Clinical Protocol #05-H-0016: Therapeutic Application of Intravascular Nitrite for Sickle Cell Disease. Open for analysis only.**

**Principal Investigator: NIH Clinical Protocol #05-H-0019: A Prospective, Multicenter, Double-Blind, Randomized, Placebo-controlled Study of Nitric Oxide for Inhalation in the Acute Treatment of Sickle Cell Pain Episode.**

**Associate Investigator: NIH Clinical Protocol #05-CC-0041: Endothelial Cell Dysfunction in Pulmonary Arterial Hypertension: Biomarkers, Mechanisms of Disease and Novel Therapeutic Targets.**

**Associate Investigator: NIH Clinical Protocol #05-CC-0062: Evaluation of Patients with Critical Illness: Intensive Care Training Protocol.**

**Principal Investigator: NIH Clinical Protocol #05-H-0088: Evaluation of the Mechanism of NO Formation and Pharmacokinetics of Systemic Nitrite Infusion. Open for analysis only.**

**Principal Investigator: NIH Clinical Protocol #05-H-0114: Evaluation of Systemic Nitrite Infusion and Its Effect on Exercise Physiology and Metabolism. Open for analysis only.**

**Associate Investigator: NIH Clinical Protocol #05-CC-0154: Are Left Ventricular Abnormalities Associated with Pulmonary Hypertension in Sickle Cell Anemia? Terminated 9/07.**

**Principal Investigator: NIH Clinical Protocol #06-H-0054: Evaluation of Synergy of Combining Hydroxyurea with Recombinant Human Erythropoietin Glycoform Alpha on Fetal Hemoglobin Synthesis in Patients with Sickle Cell Anemia.**

**Study Principal Investigator and Chairman of Steering Committee. Local Accountable Investigator and Associate Investigator: NIH Clinical Protocol #06-H-0123: Randomized, Placebo-Controlled Double-Blind, Multicenter, Parallel Group Study to Assess the Efficacy, Safety and Tolerability of Bosentan in Patients with Symptomatic Pulmonary Arterial Hypertension Associated with Sickle Cell Disease (ASSET 1). Open for analysis only.**

**Study Principal Investigator and Chairman of Steering Committee. Accountable Investigator and Associate Investigator: NIH Clinical Protocol #06-H-0124: Randomized, Placebo-Controlled Double-Blind, Multicenter, Parallel Group Study to Assess the Efficacy, Safety and Tolerability of Bosentan in Patients with Symptomatic Pulmonary Hypertension Associated with Sickle Cell Disease (ASSET 2). Open for analysis only.**

**Accountable and Associate Investigator: NIH Clinical Protocol 06-H-0165: Evaluation of Endothelial and Hemodynamic Function in HIV Associated Pulmonary Hypertension and A Phase I/II Safety and Efficacy in HIV Associated Pulmonary Hypertension.**

Accountable and Associate Investigator: NIH Clinical Protocol #06-H-N189:

**Prevalence of Secondary Pulmonary Hypertension (PHTN) in Patients with Sickle Cell Disease in Nigeria and the Role of HIV/AIDS and Endemic Parasitic Infections in the Natural History of Pulmonary Hypertension in Sickle Cell Disease.**

Accountable and Associate Investigator: NIH Clinical Protocol #06-H-0202: **Cardiopulmonary Function Assessment and NO Based Therapies for Patients with Hemolysis-associated Pulmonary Hypertension.**

Accountable and Associate Investigator: NIH Clinical Protocol #06-H-0220: **Long-term, Open-label, Multicenter Extension Study of Bosentan in Patients with Pulmonary Hypertension Associated with Sickle Cell Disease Completing a Double-blind ASSET Study (AC-052-368 or AC-052-369). Open for analysis only.**

Associate Investigator: NIH Clinical Protocol #07-CC-N007: **Examination of BNP Levels in HIV-Infected Patients.**

Lead Associate Investigator: NIH Clinical Protocol #07-H-0057: **Modifying Tolerance to Ischemic Injury in Human Atrial Tissue.**

Accountable and Associate Investigator: NIH Clinical Protocol #07-H-0177: **Treatment of Pulmonary Hypertension and Sickle Cell Disease with Sildenafil Therapy.**

Accountable and Associate Investigator: NIH Clinical Protocol #07-H-N181: **Pulmonary Hypertension and the Hypoxic Response in SCD.**

Accountable and Associate Investigator: NIH Clinical Protocol #07-H-0196: **Niacin Therapy to Improve Endothelial Function in Sickle Cell Disease.**

Medical Advisory, Accountable and Associate Investigator: NIH Clinical Protocol #07-H-N217: **Role of Nitric Oxide Scavenging by Plasma Hemoglobin and Identification of Hemolysis-associated Pulmonary Hypertension in Malaria.**

Associate Investigator: NIH Clinical Protocol # Pending: **Evaluation of Systemic Toxicity Associated with Allogeneic Peripheral Blood Stem Cell Infusion.**

**Principal Investigator: IRB # PRO09100113, NCT# NCT01137656: Storage Lesion in Banked Blood Due to Disruption of Nitric Oxide (NO) Homeostasis.**

**Principal Investigator: NCT# NCT00492531: Sildenafil Therapy for Pulmonary Hypertension and Sickle Cell Disease**

**Principal Investigator: IRB# PRO08110422: Collection of blood from volunteers and patients for studies of endothelial function and systemic inflammation.**

**Co-Investigator: IRB# PRO07030106: Inhaled Nitric Oxide for Sickle Cell Pain Crisis.**

**Animal Protocols**

**Principal Investigator: NIH Animal Protocol #H-0072: Mouse Models of Sickle Cell Acute Chest Syndrome and Ischemic Injury**

**Principal Investigator: NIH Animal Protocol #H-0073: The Effects of Nitrite on Metabolism**

**Principal Investigator: NIH Animal Protocol #H-0074: The Effects of Nitrite and Hypoxia on Mitochondrial Function**

**Principal Investigator: NIH Animal Protocol #H-0133: The Effects of Nitrite in a Murine Cardiac Arrest Model**

**Principal Investigator: NIH Animal Protocol #H-0149: Effects of Dietary Nitrite and Nitrate on I/R Injury of Heart and Liver in the Mouse**

**Principal Investigator: NIH Animal Protocol #H-0182: Circulating Blood Cell Versus Vascular Endothelial Cell Contributions to NOS-mediated Regulation of Blood Flow in Murine Skeletal Muscle**

**Principal Investigator: NIH Animal Protocol #H-0188: Determination of Tolerance Effect on Vascular Response to Nitrite and Nitroglycerin in Mouse Aortic Rings**

**Principal Investigator: University of Pittsburgh Protocol #0907049A-3: Reduction of the vasoconstrictive properties of the hemoglobin based oxygen carrier Aftershock (registered trademark) by co-infusion of Met-Aftershock-NO<sub>2</sub>.**

**Principal Investigator: University of Pittsburgh Protocol #1007625: The use of sGC activators to bypass nitric oxide scavenging by hemolysis in sickle cell disease.** Bayer.

**Principal Investigator: University of Pittsburgh Protocol # 0810498B-4: Testing a new principle for lower the blood pressure rising effect of hemoglobin oxygen carriers in a rat model of hemorrhagic shock.**

**Principal Investigator: University of Pittsburgh Protocol # 0906948-2: Hemolysis-Associated Hemostatic Activation in Sickle Cell Disease.**

**Principal Investigator: University of Pittsburgh Protocol # 1003570-2: Vasoconstrictive effects of the infusion of heme proteins or hemolyzed red blood cell solutions in a rat model and the vasodilatory effect of nitrite and drag reducing polymers.**

Principal Investigator: University of Pittsburgh Protocol # 1001850. Circulating blood cell versus vascular endothelial cell contributions to NOS-mediated blood flow and pressure regulation.

## SUMMARY OF RESEARCH ACCOMPLISHMENTS AND FOCUS

Since 1998, Dr. Gladwin's research activities have led to four scientific discoveries. The discoveries described below have resulted in more than 150 published peer-reviewed manuscripts, 25 approved human subject protocols, and more than 1,000 patient protocol enrollments at the NIH Clinical Center, during Dr. Gladwin's Tenure as an NIH Branch Chief. These investigations form the backbone of Dr. Gladwin's current work at the University of Pittsburgh's Hemostasis and Vascular Biology Research Institute and the Division of Pulmonary, Allergy and Critical Care Medicine.

(1) The discovery that the nitrite anion is a circulating storage pool for NO bioactivity (Gladwin, et al. PNAS 2000) that regulates hypoxic vasodilation (Cosby Nature Medicine 2003) and the cellular resilience to low oxygen and ischemia (Duranski JCI 2005).

(2) The discovery of a novel physiological function for hemoglobin as an electronically and allosterically-regulated nitrite reductase (Cosby, et al. Nature Medicine 2003; Huang et al. JCI 2005). These studies reveal that nitrite is a potent vasodilator in humans and is bioactivated by reaction with deoxyhemoglobin (and myoglobin) to generate NO preferentially under hypoxic conditions; they also suggest that hemoglobin has an "enzymatic" property as a nitrite reductase that participates in hypoxic vasodilation. In related translational studies, Dr. Gladwin has demonstrated that inhaled nitrite reverses hypoxic neonatal pulmonary hypertension in sheep (Hunter, et al. Nature Medicine 2004), and that infused nitrite solutions prevent post-subarachnoid hemorrhage-induced vasospasm in primates (Pluta et al. JAMA 2005) and prevent hepatic and cardiac ischemia-reperfusion injury and infarction in mice (Duranski et al. JCI 2005).

(3) The characterization of a novel mechanism of disease, hemolysis-associated endothelial dysfunction (Reiter, et al. Nature Medicine 2002; Morris et al. JAMA 2005; Minneci et al. JCI 2005; Rother et al. JAMA 2005). This work has described a state of resistance to NO in patients with sickle cell disease caused by scavenging of nitric oxide by hemoglobin that is released into plasma during hemolysis.

(4) The mechanistic, clinical, and epidemiological description of a human disease syndrome, hemolysis-associated pulmonary hypertension (Gladwin, et al. NEJM 2004). He has found that pulmonary hypertension occurs in 30% of patients with sickle cell disease, is a major cause of mortality in this population (odds ratio 10:1), and is strongly associated with high hemolytic rate, iron overload, and kidney disease.